ANDROGENS

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Biochemistry, Physiology, and Clinical Significance

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JOHN WILEY & SONS INC , NEW YORK
CHAPMAN & HALL, LIMITED LONDON

Library of Congress Catalog Card Number 55-9357

Printed in the United States of America

PREFACE

Approximately one-quarter of a century has elapsed since concentrated androgenic extracts were first prepared from testicular tissue During this time the structure of a number of androgens has been elucidated and their total synthesis achieved A great deal of theoretical information has now been documented and the androgens have become definitive important therapeutic agents It has been our intention to bring all this information together in one volume so that the student (medical and graduate) the clinician and the research worker can quickly get a rounded picture of all phases of the subject matter ranging from the biochemistry of androgenic compounds to their significance in clinical medicine For those individuals who desire a more precise knowledge of the steroids a detailed section is included which deals with steroid nomenclature This is coupled with a section in the appendix which lists the structural formulae of each steroid mentioned in the text and tables This arrangement we hope should lighten the burden of the student and guide the clinician with the least trauma through this often confusing subject

The early studies of the isolation of androgens from tissues and urine are now classical works Most of the details are included in this book not only because of their bearing on the characterization of certain androgenic compounds but because some of the historical aspects are of considerable interest

We hope that our book will be of particular value to men of medicine both the general practitioner and the specialist Androgens by virtue of their diverse roles in normal physiology must be considered in many medical specialties The internist the clinical endocrinologist the pediatrician the urologist the gynecologist the gerontologist and the oncologist are constantly confronted with problems involving androgens and androgen therapy The theoretical and practical aspects are herein documented

The summary of the literature on urinary androgen and 17 keto steroid excretion including interpretations should serve as an aid for both diagnosis and prognosis This is perhaps the most complete and

systematic summary available And for those individuals who do not have ready access to all the literature we have included in the appen dices the detailed directions for the preparation of urinary extracts suitable for analysis together with detailed directions for the biological and chemical assays

The literature on androgens is enormous and we cannot claim that every report is herein described digested and documented Every effort has been made to consult as many of the papers as possible and we hope that at least a partial success was achieved

Many friends and colleagues graciously assisted us in many phases of the work and it is with deep pleasure that we record our indebted ness Drs Irene T Kline Annabelle M Miller Sara Schiller Betty L Rubin Hans Hirschmann Kenneth Savard and Erwin Schwenk kindly read parts of the manuscript and made helpful suggestions Special thanks are due Mrs R I Dorfman and Miss Phyllis Galanto for their enormous efforts in typing and checking the manuscript as well as in reading proof and doing the infinite number of chores that must be taken care of in the publishing of a book We are also grate ful to Miss Frances Callaghan for assistance in typing a considerable portion of the manuscript Dr Banay librarian of the Worcester State Hospital gave freely of his knowledge and time so that the references could be accurate We thank him for this help but remind the reader that inaccuracies of literature citation as is true of all errors and omissions of pertinent facts are not intentional and are solely the responsibility of the authors

RALPH I DORFMAN
REGINALD A SHIPLEY

January 1956

FOREWORD

In this volume Dr Dorfman and Dr Shipley have provided endo crinologists with the kind of exposition of their subject that has been sought for many years So vast has become the field of endocrinology that no single book or author can hope to consider adequately its many faceted aspects Those who do attempt this task succeed only in furnishing us with cursory summaries of the subject or volumes in which some areas are given relative overemphasis and others are slighted—usually in proportion to the author s or authors particular interests Thus we must recognize the necessity for comprehensive considerations of relatively delimited areas by authors who possess extensive experience and competence in those areas In the present instance Dr Dorfman and Dr Shipley have brought their skills and knowledge to a thorough consideration of the androgenic hormones

The androgenic hormones more commonly but less accurately known as the male sex hormones are now known to have functions other than the stimulation of such structures as the secondary sex characteristics of the male organism The female too shares in the beneficial effects provided by this hormone or hormones since it has become more and more evident that important aspects of protein anabolism in both sexes are regulated by androgenic substances In as much as the proteins have far reaching importance in essentially all phases of physiologic economy it is apparent that thorough regard for the factors controlling their disposition should have our interest and attention Today our comprehension of the nature of the andro genic substances and the role they play in the spectrum of physiologic mechanisms has been the product of studies involving biological or ganic and synthetic chemistry physiology bacteriology enzymology cytology and clinical medicine Each of these has contributed its measure to the proper appreciation of the important function played by the androgens in stimulating regulating and modifying a multitude of mechanisms important to the physiologic economy

This emphasis on the extra sexual sphere of importance of the an drogens by no means belittles the role such substances play in provid

ing for sexual normality Indeed the existing evidence suggests that not only normal function of the male accessory organs of reproduction but also the production of male gametes depend upon an adequate level of androgen Such a far reaching significance is not applicable to the female but even in her case we have reason to believe that libido is influenced materially by androgenic hormone Thus the evidence mounts and indicates that these substances are of importance in perpetuating the species not only by assuring the advent of new organisms but also by providing for the development of those organisms to at least the age of reproduction when they are ready to begin the cycle again

The far reaching significance of androgenic function deserves the kind of careful and thorough consideration that has been accorded the subject by Dr Dorfman and Dr Shipley The reader of this book is certain to obtain from it a fuller and clearer picture of the nature and function of the androgenic hormones

WARREN O NELSON

Rockefeller Institute
January 1956

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science and the scientific attitude was not only undesirable, but impossible

This conflict of views led to considerable discussion of the term reason The speaker from U S A expressed his con cern that the Conference should even appear to disparage the place of reason in life and education Right reason was their shield against vague emotionalism, anti intellectualism and such excesses as are called to mind by the Nazi phrase thinking with the blood This timely protest gave rise to a more philosophical, though desultory, discussion of reason, at later sessions A French member warmly agreed that reason was in its true sense the mark of man, autonomous and divinely created to whom God had given, in St Thomas phrase the dignity of being a cause (la dignite de cause) We must distinguish the Conference agreed between this sense of reason and the sense in which it was applied to the purely intellectual element in man unnaturally divorced from the rest of his personality Was not this, roughly speaking, the difference between Pascal and Descartes? Human reason in its best sense was a very different thing from the hard over logical rationalism of the Marxist for whom even history was subject to a single rigid interpretation this led to propaganda intolerance and persecution We needed to regain a sense of the mystery of history That lower kind of reason, said the French speaker could be compared to a lemon squeezer it crushes the ideas that are fed to it and then throws them away

The educational bearing of these reflections was thoroughly discussed in the second half of the Conference, but before we had come to the end of the first half, mention of the alleged intolerance among scientific rationalists led to some discussion of tolerance and hence of religion a subject which had not appeared prominently in most of the papers submitted The debate about reason had been carried on mostly by Western delegates but now Indian members expressed their views Tolerance was only too clearly a virtue which most men needed to learn, but tolerance tended by easy steps towards apathy and how far should we tolerate intolerance? No answer was found to this familiar conundrum An Indian speaker maintained that tolerance was not enough tolerance too often implied condescension, but the tolerance worth

having combined appreciation of the other point of view with a deep conviction of one s own

There was clearly suspicion of religion among some members One speaker sketched an ideal community with a class of leaders at its head Pleading for the qualities of charity sympathy and self sacrifice he surprised some of us by saying that for his highest class he would have no religion at all History showed that religion had been generally a divisive force If some religion was thought necessary for the two less cultured classes of the State it must not be held blindly or it was bound to become fanatical and intolerant

One of the Western delegates wondered why religion should be subject to this distrust in an Eastern philosopher's mind He would have thought, on the contrary that India is perhaps the first place in the world where philosophy is the least separable from religious sources That is at least what Western thought looks for in India nowadays religious philosophy fit for uniting innumerable souls rather than for disuniting them and setting them against each other Would not the East fail in its mission if, on the contrary it tended to dissociate religion from philosophy?

The Chairman then suggested that a misunderstanding had perhaps slipped into the debate We must not he said confuse religion and fanaticism The most justified warnings against intolerance do not apply to religious thought when it is considered as an element of life and spirit The delegates agreed with him that one must distinguish religion whose influence may be of great importance in the life of ideas and fanaticism which gives rise to war among minds, if not among nations

The educational part of our Symposium broadly speaking turned on two topics the impact on education of (a) science especially in the West (b) democracy especially in the East The discussion opened with a commentary by the American speaker on his paper already circulated and his speech formed a suitable transition from the more general subject to the more specialized He reiterated the danger, in his view of a flight from reason But he realized too the danger of education if the approach were too rigidly rationalistic The U S.A had many practical problems to solve and perhaps there was a risk that education should become preoccupied with

process and unduly suspicious of 'absolutes Two schools of thought about education could be distinguished along these lines Further examination of the philosophic foundations of these schools might discover basic agreements between them and provide the foundations for the resolution of their practical differences The speaker from the U S A pointed out that another aspect of American thought, namely, the principle of tolerance of opposed philosophic positions was important as a basis both for the avoidance of practical conflicts and the discovery of theoretic agreements

Subsequent speakers were divided on this issue of the place of science and the scientific approach in education An Eastern member deplored science entirely as far as he could see, its main uses in the modern world were either industrial or militaristic and both were regrettable Others came to the defence of science it was absurd to regard it as purely utilitarian the ideal of knowledge for its own sake could be predicated of the scientist as well as of the humanist Nor was it fair to say that the influence of science in education was bound to be materialistic This may have been so at the end of the nineteenth century but, since 1900 there were many indications e g, in the philosophy of Bergson that conscious logical reason no longer held its old supremacy in man s personality, even in the eyes of scientists

These considerations led other members to make a special plea for the association of philosophy with the teaching of science at the university stage, but it must be real philosophy, taught by philosophers, not expounded in books called Histories of Philosophy which only made students think they understood philosophy when they had merely studied the lives of philosophers The Turkish speaker pointed out that there are two sorts of philosophical teachings a cinematographic view of doctrines, which leads to scepticism, and a conception of the evolution of human thought through successive improvements and expansions which is but the history of problems and is never prejudicial

The Conference in general concurred with the American speaker when he claimed that the educator must do two things (a) train the specialist for his work (b) (even more important) train specialist and non specialist alike to be thoughtful citizens

At a later session the English member introduced a plea

for humanism was not this the approach required an approach which was more than the mere imparting of a mere technique, but at the same time was more concrete than instruction in philosophical absolutes The humanities" were not simply an alternative course of study to science as they were too often regarded in English schools the humanities were part of every man s birthright But much depended on the quality of the teacher and here perhaps the West might learn from the East with its deep traditional reverence for the personality of the wise teacher Science teachers today were too often content to communicate a technique the humanist communicated his whole personality Humanist education was not mere vague emotion it led to its own kind of knowledge less calculable and exact than scientific knowledge, but for most men even more important

The Egyptian speaker would interpret humanism in another sense the whole of the moral and intellectual principles which govern man as an individual or as a member of a community It is a human inheritance which has been formed throughout the ages and amid the various civilizations It is neither purely Eastern nor purely Western it is only international There should be established a complete scale of these international values which ought to be religiously respected and observed everywhere Otherwise a society of nations would not be of much avail Let us beware also of certain national values which incline to prevail over international values It is to be feared that a domineering nationalism would not yield its place to internationalism

The above résumé will give some idea of the disjointed but lively discussion on the question what part was to be played by science in modern education Some concrete questions were also asked by one or two Western members and answered by one of the Indian professors He agreed that the university system in India was too much at the mercy of examinations for this reason he would like to see some part of the university course (e g general lectures on philosophy especially for scientists) not tested by examination He thought that the highest standards in the university were prevented from being attained owing to the economic value attached to a degree Asked whether in India as in the West the superior education gained by the young graduate isolated him

from his family circle, he replied that this certainly was a danger in India where the family circle was more integral to society than it was in the West Questioned about the Hindu view of history he admitted that any philosophy which regarded time as unreal could not attach much importance to the study of history but this was not his own view on the matter

The second topic which took up most of the time remaining to the Conference, was the impact of democracy on education particularly in India The question had already been raised at an earlier session whether the new democracy was really capable of absorbing and profiting by the higher education represented by the universities A European delegate had been asked in view of a remark made in his paper, whether he thought that the great majority in any country were doomed to exclusion from the benefits of higher education He replied that he certainly would not say that but added candidly that he believed that it would be a long time before the new masses could be effectively linked to what was an ancient and aristocratic tradition of culture A similar attitude received some support from a later contribution by an Indian speaker His sketch of an ideal community with its three classes was strongly reminiscent of Plato, a fact in itself indicative of a link between East and West, and he had a somewhat Platonic fear of democracy A man, he said was only fully man in proportion as he could rise to appreciation of the higher values there were inevitably many who had neither the desire nor the power to rise were they in reality very different from animals? This view could hardly be taken as typical of the Conference as a whole, but it was a salutary warning against the facile idealism which sometimes accompanies the champions of democratic education At any rate it was pointed out by another speaker from the East if universities did not discriminate among their applicants, they would soon cease to be universities in the true sense and become degree getting machines A third Eastern speaker pleaded for more attention to the imagination and aesthetic qualities of the child in the early stages of education Concentration on the intellectual abilities which enable a youth to pass examinations was one sided and would lead to intellectual arrogance

An Indian speaker, formerly a professor of philosophy, now in the service of the Ministry of Education of India in his address followed the lines of his circulated paper science had brought to mankind new contacts between nations on a wide scale In respect of space and time, the world was more nearly a unity than ever before Cultural unity must be fostered to match it We must create a common ideological background not only for the educated few but for the mass of men That men s opinions *could* be shaped and guided was only too apparent from the effects of mass propaganda for propaganda democracy must substitute education Universities were not solely a matter of higher education on them largely depended the supply and quality of teachers for the schools and without devoted teachers no system, however well organized, could flourish or become the basis of the universities

There were obstacles to true democracy which only education could remove the myth of racial superiority the nationalist presentation of history We lived in an age of revolutions, these were bound to come and only education, acting as mediator between tradition and experiment, could prepare men for revolution without violence and bloodshed The first effects of education in an immature democracy might be to isolate the young student from his home traditions and to give him as it were two standards But the educational process once started, must press on until the student had attained an integrated outlook only by the cultural integration of the individual student could we achieve an integrated society and at length an integrated world

Mr Thomas speaking for Unesco assured the Conference that much of what was to be recommended had already been undertaken by Unesco An enquiry was being conducted into the teaching of philosophy and he was glad to find the Conference suggesting a closer association between philosophy and science at the university level Moreover Unesco was soon to publish a history of the scientific and cultural development of mankind which might go far to meet Professor Kabir s plea for an integration of thought between the nations

The above account of our discussions is designed to cover only what was said at the conference table It will be seen from the Appendix that some members contributed learned and illuminating papers e g, Professors Glasenapp and

Ulken which had been read with profit by all members of the symposium, but did not lend themselves to general discussion

GENERAL CONCLUSIONS

It will be evident from the foregoing resume of our discussions that they were grouped round individual papers already circulated, and each contributor was then asked to amplify his point of view at the conference table Speakers were free to develop their thoughts as they wished and were not asked to provide answers to specific questions Nevertheless a number of conclusions emerged though they were not expressed in the form of unanimous or majority resolutions

Together with the basic document there had been circulated an Addendum entitled Some crucial questions [1] The Conference could not have had the time to answer all these questions, but the Addendum printed in the Appendix may serve as a frame in which to embody our conclusions What follows was in substance read to the Conference at its last meeting and general agreement was given to its publication This series of questions in the Addendum did not emphasize the divergence between East and West but was constructed with the assumption that, on the broad issues about the concept of man, his nature and his education, members might not indeed be unanimous but their differences would not correspond to the division between East and West So indeed it turned out at the Conference itself Within the first few sessions it had become a truism to say that the conventional distinction between the active West and the contemplative East was fallacious There were divergences which followed an East West division and they appear in this expression of our views, but it would give a wrong perspective to allow undue prominence to such divergences although they will be noted in their place (References are made to the sections of the Addendum)

Section 1 The relationship between religion and the spiritual and ethical life It was generally agreed that in India religion was

[1] See Appendix I

more truly the basis of ethics and philosophy than it was in the West where many books on ethics have been written with no reference to religion at all, but though this applies to India, it is not true of other parts of the East, e g China Both Eastern and Western members expressed the fear of religion as a divisive influence better no religion than one that was fanatical and intolerant

Section 2 Man s power to master nature by technology Here the Conference was divided but not according to an East West division Many realized the deadening effect of a machine age on the soul of man, and the damage done to education if it was reduced to the mere communication of a scientific technique But it was claimed by representatives from the West and India alike that science had brought health and life itself to thousands and must not be undervalued Nevertheless, if it were true that scientific reason had enabled man to master the world, there were signs that it might enslave man himself and this was too high a price to pay for any conquest of nature

This conclusion is closely linked with the issue raised in *Section 3 The limits to be assigned to the power of the intellect intellectual learning and the cultivation of the whole man* Here there was agreement even among those who set a high value on reason that the intellectual element was only one part of man s nature and some feeling that, particularly in the West it was tending to usurp excessive authority Members agreed in a plea for educating the imagination and the spirit as well as the mind (here aesthetic values would play a vital part see *Section 4*) Most members of the Conference felt that only thus could a student s mind be integrated and without in ... on of the individual there could be no integration of a

... *5 Conceptions of education and the idea of equality the ... ation of all in cultural life* From the earliest stages educa ... ion should emphasize the dignity of the individual whatever ... social status the Gandhian conception of basic education ... ould be developed Nationalist tendencies in education ... , in the teaching of history, which assumed the

superiority of one race over another, were to be universally discouraged One speaker with a measure of agreement from others asserted that even so it would inevitably be a long time before the mass of men could be linked to an old tradition of aristocratic culture

Section 6 What part can national and international institutions play in a new humanism ? Humanism of some kind was a basic element in all true education providing a counter weight to excessive technology in the West and in the East fortifying an outlook that might become unduly vague and other worldly Educational institutions both in East and West and international organizations could play an important part in this matter The East might supply new classics as required for the new humanism

Section 6 The value of patriotism and the danger of nationalism There was general concurrence in stressing the evil of aggressive nationalism, but even humanism must begin by being what one speaker called patriotic humanism The young must begin with their own country and their own language It was a contemptuous attitude to other peoples rather than a pride in one s own that was injurious

Section 8 Tolerance While recognizing tolerance as a virtue which the world still needed to learn, the Conference was alive to the dangers of a tolerance which was hardly to be distinguished from apathy tolerance with conviction, and without condescension, was the only effective kind

Section 9 Time and eternity On this topic, members really were divided, and nothing approaching a conclusion was reached To the Western mind time was a reality and history a study of basic importance To some Eastern thinkers though not to all, time was an unreality and hence history was a subject of little importance although this did not represent the views of Islam which had produced notable historians

Section 10 The importance of a philosophy of human labour Members were in agreement with one speaker (see the section on work in Mr Beguin s paper) that work today, owing to techni

cal devices, was losing its old respected place in man's life To rediscover an ethic of work was a primary task for philosophers today

Section 12 The education of the full human being and the training of the specialist After full and varied discussion, the Conference agreed that while specialists were more than ever necessary in the modern world a specialized training was often no education at all Specialists and non specialists alike should study the humanities as part of their full education as men in particular, philosophy should be imparted in lectures and classes (preferably *not* for examination) to all students of science The philosopher could learn from the scientist, but could also show the scientist some limitations of science

These views represent some conclusions of the Symposium irrespective of the difference between East and West On that particular subject the Conference was broadly agreed that

1 The difference has been over emphasized in popular thought
2 The East was by no means synonymous with India
3 Certain differences due to geography climate, etc, must always remain and could not be changed
4 Even so, the typical *attitudes* of Eastern and Western man are products of evolution and in the process of time could be modified by cultural contacts
5 Such contacts are now possible on a scale unknown before and should be encouraged by every means available
6 We take hope from the reflection that wars and world conflicts have not arisen from differences of civilization such as are represented by East and West, but between the uncivilized and fanatical minorities within a single civilization It was to eliminate such uncivilized minorities by means of education that East and West might co-operate

RECOMMENDATIONS

That contact between East and West should be encouraged by a series of conferences held both in Eastern and Western centres to be attended by groups representing philosophy, science arts and education

That suitable books should be produced for use in schools and universities, both in East and West, giving an account of the teaching of the 'Prophets and leaders of religious and philosophical thought In this connexion the Conference noted with satisfaction the attempt made by leading educationists, especially the British for the study of the ethical philosophical and religious classics of the world (The document on the subject was circulated to the members of the Conference by the courtesy of the Chairman)

That the classics of the East should be better known in the West than they are at present, and that to this end Unesco should establish a committee to choose such classics and to *supervise their publication*

That the teaching of science should at all stages be more closely associated with the teaching of philosophy

That education especially in its early stages should give more scope to development of the imagination and aesthetic sensibilities of children

That history as taught in schools should be re orientated away from a nationalist outlook, and that the publication of historical textbooks should be supervised by joint committees representing different nationalities

That the work already undertaken by Unesco in the educational field, such as providing information on different national types of education and establishing a panel of experts available for advice on the subject, should be further encouraged

Addresses delivered at the Formal Opening Session of the Symposium

Presidential Speech

by

H E Maulana Abdul Kalam Azad

Minister of Education of India

Friends,[1]

On behalf of the Government of India and on my own behalf I have great pleasure in welcoming you all to this Symposium

Unesco has, since its inception, been organizing seminars discussion groups and symposia for considering various problems that affect the relations of nations and countries and for creating better understanding through the exchange of knowledge and experience in many fields This Symposium is concerned with an even more fundamental issue Today, philosophers of East and West have met to discuss the concept of man himself Who can deny that this issue is the basic one of the modern age and on its satisfactory solution depends the future of man I am therefore specially happy to welcome you here to this ancient land of philosophers and seers I earnestly hope that the spirit of India with its long traditions of wisdom and spirituality will inspire all your deliberations

I

In the last 6,000 years or more the human being has travelled over a vast region from his early beginnings in primitive society This period has seen man overcome many hidden obstacles and meet the challenge of inanimate nature and the animate world In spite of all the vicissitudes which man has had to face during this period, there has, on the whole been continuous and steady progress in wresting from nature some of her greatest secrets Veil after veil has been torn asunder

[1] This speech was delivered in Hindi.

from the hidden face of nature and secrets that are still un known are yielding to his quest

While man s triumphant progress in unveiling the face of nature has been steady and continuous can we say with equal confidence that he has succeeded in unveiling the lineaments of his own self? Can we say that after 6,000 years of quest of the real, man today sees himself as he essentially is? I think you will agree that we have to make a sad confession in this matter The mirror that man has fashioned reflects all aspects of the world but not his own inner self We have to admit that man has not yet been able to form a clear picture of his own nature The secrets of the universe are clearer to him than the secrets of the self For some 3 000 years or more, philosophers have again and again asked what is man, whence does he come and whither does he go? The questions still remain largely unanswered It is obvious that man cannot achieve a satisfactory solution of the problems of the individual, society, nations and international relations till he knows clearly the nature of his own self and determines what the place of man is in the vastness of the universe

The basic issue before you is the consideration of this prob lem You have met to discuss the concept of man as it has been enunciated by thinkers in the East and the West I would at the very beginning like to emphasize that in speak ing of the East and the West, we are thinking only of certain special features in the thought of these regions This cannot and does not mean that there are not large areas of common and agreed ground Man all over the world has adopted common methods of reasoning and thought The human reason is one and identical Human feelings are largely similar The human will operate in more or less the same manner in similar situations everywhere It is therefore natural that the human s way of looking at himself and the world is largely common in different parts of the world His attitudes towards the unknown mysteries of existence are also largely similar The Greeks who looked with admiration and awe upon the peaks of Olympus shared the same feelings as the Indians who meditated in the valleys of the Himalayas and looked upon their eternal snows

In spite of large areas of agreement, human minds in differ ent regions of the world have adopted a different approach

to some of their common problems Even where the approach has not been different, there has been a tendency to place a different emphasis on the different aspects of common prob lems and common solutions No two situations are exactly alike It was inevitable that people in different regions should pay greater attention to different aspects of common problems It is on account of such differences in emphasis that we des cribe a particular mode of thought as characteristic of a particular nation or region It is from this point of view that I will try to formulate what are the differences that distinguish the East from the West I think you will all agree that even where the solutions are similar in pattern and outline there are differences in shade and colour which justify us in calling some of the solutions Eastern and others Western

There are, as I have said many points in common between the views of philosophers in the East and the West but the emphasis is different in India Greece and China as strikes us from the very beginning of recorded history In India, the emphasis of philosophy has on the whole been on the inner experience of man Philosophers here have sought to under stand man s inner nature and in this pursuit have gone beyond the regions of sense intellect and even reason and sought to assert the identity of man with a deep hidden reality In Greece the philosopher has been interested mainly in under standing the nature of the world outside He has sought to determine the place of man in the outer world His view has therefore been on the whole more extrovert than in India In China, on the other hand philosophers have not worried about the inner nature of man nor about external nature but have concentrated on the study of man in relation to his fellows These differences in orientation have exerted a profound influence on later developments of philosophy in each of these regions We find therefore that there are striking differences in their respective concepts of man

The Greeks approached the concept of man from an external point of view Hence we find that from the earliest times Greek philosophy devotes far greater attention to what man does rather than to what man is It is true that some of the earlier Greek philosophers thought of man as essentially a spiritual entity, and we find that this is perhaps the prevailing mode of thought till the time of Plato With the advent of Aristotle

there began however, a new orientation in which the attention is diverted from the idea of man to man s activities in the world here and now Under the influence of Aristotle who defined man as a rational animal philosophy became more positive In course of time this positive empirical and scientific attitude became the prevailing climate of thought in the West Rationality distinguishes man from other animals, and it is through the exercise of rationality that he has advanced far beyond his early animal origin Nevertheless, he remains essentially and fundamentally a progressive animal Rarely has this thought been expressed so beautifully as by the German philosopher Riehl While he admits that man has descended from the animal, he points out that he has now reached a stage where he must look above and not below He is the only animal that stands erect and can continue to do so only if his look is upward God is the goal towards which man must strive if he is to retain his present stature

It is true that the influence of Christianity and the persistence of the Platonic tradition remained a powerful element in European thought Thus we find that the scholastics in the medieval ages were at times more theologians than philosophers Even in the modern period there is a strong religious idealistic strain in European thought Since the beginning of the modern age this strain has however steadily yielded place to a philosophical outlook dominated by the concepts of science The triumphant progress of science began in the seventeenth century and increased man s power over nature The success of science dazzled the Western mind and induced a faith in its unfailing efficacy The West sought to apply the concepts and methods of science in all fields of human experience and treat man also as an object among other objects In course of time a materialistic and scientific temper became the pervasive outlook of the West We find a culmination of this development in the nineteenth and the twentieth centuries Darwin sought to establish that man is descended from animals while Marx argued that his mentality is largely the resultant of his material environment Freud in the twentieth century went a step further and taught that not only is man descended from animals but his mentality retains even today traces of his animal origin

As opposed to this conception of man as a progressive animal,

~ find in the East a completely different concept of man ?ne East has from the very beginning emphasized man's spirituality The contemplation of the inner reality ' man gave rise to the philosophy of Vedanta in India and ' in Arabia This spiritual concept of man has deeply uenced the mentality of man throughout the East and is ot unknown even in the West According to this outlook we annot understand the essence of man if we regard him as only material entity The real nature of man can be understood ly if we conceive of him as an emanation of God There was i Eastern philosophy a strong pantheistic strain In different ools of Indian philosophy, all things are regarded as ex ~ of God s being but even then man belongs to a ' category For he is the highest manifestation of God s ieing In the words of the Gita (XI 18)

> *Thou art the Imperishable, the Supreme to be realized*
> *Thou art the ultimate resting place of the universe*
> *Thou art the undying guardian of the eternal law*
> *Thou art the Primal Person*

, y we find that according to the Sufis, man is a wave of boundless sea that is God He is a ray of the Sun that is od Man can regard himself as different from the Eternal eing only so long as his vision is clouded by the evil of gnorance Once there is enlightenment, all these distinctions e and man recognizes himself as a moment in the of the eternal

The concept of man which the East has framed regards him is not merely an animal superior to all earthly creatures but essentially different in nature Man is not first among equals *it has a being which is higher than that of any other creature* is not only a progressive animal but reveals in his being lineaments of God Himself In fact his nature is so high and elevated that nothing higher is conceivable to human eason In the words of the Chhandogya Upanishad (9 4)

That is Reality That is Atman (Soul) That art thou

doctrine has also been beautifully expressed in Arabic

Man arafa nafsahu faqad arafa rabbahu [1]

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[1] He who knows himself knows God.

The same principle, when further developed, gives rise to the idea that man is not an isolated individual but contains in himself the entire universe In the words of the Gita (XI 7)

> *Here today behold the whole universe moving and unmoving and what ever else thou desirest to see O Gudakesa (Arjuna), all unified in My body*

A Sufi poet has expressed the same concept in the Arabic verse

> *Watahsab annaka jarmun saghir*
> *Wa fika antavi alemun akbaru* [1]

It will be readily agreed that there can be no higher concept of man God marks the highest limit of human thought By identifying man with God, the Eastern concept of man elevates him to godhead Man has therefore no other goal but to re establish his identity with God He thus becomes superior to the entire creation

II

We have till now discussed the concept of man from the point of view of the philosophies in the East and the West We now wish to review briefly what religion has to say on the question If we consider the attitude of Judaism and Christianity, we find a clear statement in the Old Testament that God created man in His own image From this it would follow that man shares in the attributes of God A strong element of spiritual mysticism has characterized the attitude of Christianity and has acted as a check to the predominance of extreme material istic tendencies

In Islam we find traces of the influence of the same outlook In fact the Koran has gone a step further in its exaltation of man The Koran proclaims that not only is man created in the image of God but is His regent on earth In speaking of the creation of Adam, God says (2 29)

> *Inni jaelun fil arde khalifat* [2]

1 Thou thi k t th t thou rt a small body th k owest t that a u ers gr at than the phys l w ld i ta ed n th
2 I want to t my ice y a th

Presidential Speech

by

H E Maulana Abdul Kalam Azad

Minister of Education of India

Friends,[1]

On behalf of the Government of India and on my own behalf I have great pleasure in welcoming you all to this Symposium

Unesco has, since its inception, been organizing seminars discussion groups and symposia for considering various problems that affect the relations of nations and countries and for creating better understanding through the exchange of knowledge and experience in many fields This Symposium is concerned with an even more fundamental issue Today, philosophers of East and West have met to discuss the concept of man himself Who can deny that this issue is the basic one of the modern age and on its satisfactory solution depends the future of man I am therefore specially happy to welcome you here to this ancient land of philosophers and seers I earnestly hope that the spirit of India with its long traditions of wisdom and spirituality will inspire all your deliberations

I

In the last 6 000 years or more the human being has travelled over a vast region from his early beginnings in primitive society This period has seen man overcome many hidden obstacles and meet the challenge of inanimate nature and the animate world In spite of all the vicissitudes which man has had to face during this period there has, on the whole been continuous and steady progress in wresting from nature some of her greatest secrets Veil after veil has been torn asunder

[1] This speech was delivered in Hindi.

from the hidden face of nature and secrets that are still ı known are yielding to his quest

While man's triumphant progress in unveiling the face nature has been steady and continuous, can we say with eq confidence that he has succeeded in unveiling the lineam of his own self? Can we say that after 6,000 years of ques the real man today sees himself as he essentially is? I th you will agree that we have to make a sad confession in matter The mirror that man has fashioned reflects all asp of the world but not his own inner self We have to admit t man has not yet been able to form a clear picture of his c nature The secrets of the universe are clearer to him than secrets of the self For some 3 000 years or more philosopl have again and again asked what is man whence do come and whither does he go? The questions still re largely unanswered It is obvious that man cannot achie satisfactory solution of the problems of the individual soci nations and international relations till he knows clearly nature of his own self and determines what the place of ı is in the vastness of the universe

The basic issue before you is the consideration of this p lem You have met to discuss the concept of man as it been enunciated by thinkers in the East and the We would at the very beginning, like to emphasize that in sp ing of the East and the West, we are thinking only of ce special features in the thought of these regions This ca and does not mean that there are not large areas of com and agreed ground Man all over the world has ado common methods of reasoning and thought The hu reason is one and identical Human feelings are largely si The human will operate in more or less the same mann similar situations everywhere It is therefore natural tha human s way of looking at himself and the world is lai common in different parts of the world His atti towards the unknown mysteries of existence are also la similar The Greeks who looked with admiration and upon the peaks of Olympus shared the same feelings a Indians who meditated in the valleys of the Himalayas looked upon their eternal snows

In spite of large areas of agreement, human minds in d ent regions of the world have adopted a different app

to some of their common problems Even where the approach has not been different, there has been a tendency to place a different emphasis on the different aspects of common problems and common solutions No two situations are exactly alike It was inevitable that people in different regions should pay greater attention to different aspects of common problems It is on account of such differences in emphasis that we describe a particular mode of thought as characteristic of a particular nation or region It is from this point of view that I will try to formulate what are the differences that distinguish the East from the West I think you will all agree that even where the solutions are similar in pattern and outline there are differences in shade and colour which justify us in calling some of the solutions Eastern and others Western

There are, as I have said, many points in common between the views of philosophers in the East and the West but the emphasis is different in India, Greece and China as strikes us from the very beginning of recorded history In India the emphasis of philosophy has on the whole been on the inner experience of man Philosophers here have sought to understand man s inner nature and in this pursuit have gone beyond the regions of sense intellect and even reason and sought to assert the identity of man with a deep hidden reality In Greece, the philosopher has been interested mainly in understanding the nature of the world outside He has sought to determine the place of man in the outer world His view has therefore been on the whole more extrovert than in India In China, on the other hand philosophers have not worried about the inner nature of man nor about external nature but have concentrated on the study of man in relation to his fellows These differences in orientation have exerted a profound influence on later developments of philosophy in each of these regions We find therefore that there are striking differences in their respective concepts of man

The Greeks approached the concept of man from an external point of view Hence we find that from the earliest times Greek philosophy devotes far greater attention to what man does rather than to what man is It is true that some of the earlier Greek philosophers thought of man as essentially a spiritual entity, and we find that this is perhaps the prevailing mode of thought till the time of Plato With the advent of Aristotle,

from the hidden face of nature and secrets that are still un known are yielding to his quest

While man's triumphant progress in unveiling the face of nature has been steady and continuous can we say with equal confidence that he has succeeded in unveiling the lineaments of his own self? Can we say that after 6 000 years of quest of the real man today sees himself as he essentially is? I think you will agree that we have to make a sad confession in this matter The mirror that man has fashioned reflects all aspects of the world but not his own inner self We have to admit that man has not yet been able to form a clear picture of his own nature The secrets of the universe are clearer to him than the secrets of the self For some 3 000 years or more, philosophers have again and again asked what is man whence does he come and whither does he go? The questions still remain largely unanswered It is obvious that man cannot achieve a satisfactory solution of the problems of the individual society nations and international relations till he knows clearly the nature of his own self and determines what the place of man is in the vastness of the universe

The basic issue before you is the consideration of this prob lem You have met to discuss the concept of man as it has been enunciated by thinkers in the East and the West I would at the very beginning like to emphasize that in speak ing of the East and the West, we are thinking only of certain special features in the thought of these regions This cannot and does not mean that there are not large areas of common and agreed ground Man all over the world has adopted common methods of reasoning and thought The human reason is one and identical Human feelings are largely similar The human will operate in more or less the same manner in similar situations everywhere It is therefore natural that the human s way of looking at himself and the world is largely common in different parts of the world His attitudes towards the unknown mysteries of existence are also largely similar The Greeks who looked with admiration and awe upon the peaks of Olympus shared the same feelings as the Indians who meditated in the valleys of the Himalayas and looked upon their eternal snows

In spite of large areas of agreement human minds in differ ent regions of the world have adopted a different approach

we find in the East a completely different concept of man The East has from the very beginning emphasized man s intrinsic spirituality The contemplation of the inner reality of man gave rise to the philosophy of Vedanta in India and Sufism in Arabia This spiritual concept of man has deeply influenced the mentality of man throughout the East and is not unknown even in the West According to this outlook we cannot understand the essence of man if we regard him as only a material entity The real nature of man can be understood only if we conceive of him as an emanation of God There was in Eastern philosophy a strong pantheistic strain In different schools of Indian philosophy, all things are regarded as expressions of God s being but even then man belongs to a *special category* For he is the highest manifestation of God s being In the words of the Gita (XI 18)

Thou art the Imperishable the Supreme to be realized
Thou art the ultimate resting place of the universe,
Thou art the undying guardian of the eternal law
Thou art the Primal Person

Similarly we find that according to the Sufis man is a wave of the boundless sea that is God He is a ray of the Sun that is God Man can regard himself as different from the Eternal Being only so long as his vision is clouded by the evil of ignorance Once there is enlightenment all these distinctions dissolve and man recognizes himself as a moment in the being of the eternal

The concept of man which the East has framed regards him as not merely an animal superior to all earthly creatures but as essentially different in nature Man is not first among equals but has a being which is higher than that of any other creature He is not only a progressive animal but reveals in his being the lineaments of God Himself In fact his nature is so high and elevated that nothing higher is conceivable to human reason In the words of the Chhandogya Upanishad (9 4)

That is Reality That is Atman (Soul) That art thou

This doctrine has also been beautifully expressed in Arabic

Man arafa nafsahu faqad arafa rabbahu [1]

[1] He who knows himself knows God.

there began however a new orientation in which the attention is diverted from the idea of man to man s activities in the world here and now Under the influence of Aristotle who defined man as a rational animal philosophy became more positive In course of time, this positive, empirical and scientific attitude became the prevailing climate of thought in the West Rationality distinguishes man from other animals, and it is through the exercise of rationality that he has advanced far beyond his early animal origin Nevertheless, he remains *essentially and fundamentally a progressive animal* Rarely has this thought been expressed so beautifully as by the German philosopher Riehl While he admits that man has descended from the animal he points out that he has now reached a stage where he must look above and not below He is the only animal that stands erect and can continue to do so only if his look is upward God is the goal towards which man must strive if he is to retain his present stature

It is true that the influence of Christianity and the persistence of the Platonic tradition remained a powerful element in European thought Thus we find that the scholastics in the medieval ages were at times more theologians than philosophers Even in the modern period, there is a strong religious idealistic strain in European thought Since the beginning of the modern age this strain has however, steadily yielded place to a philosophical outlook dominated by the concepts of science The triumphant progress of science began in the seventeenth century and increased man s power over nature The success of science dazzled the Western mind and induced a faith in its unfailing efficacy The West sought to apply the concepts and methods of science in all fields of human experience and treat man also as an object among other objects *In course of time a materialistic and scientific temper became* the pervasive outlook of the West We find a culmination of this development in the nineteenth and the twentieth centuries Darwin sought to establish that man is descended from animals while Marx argued that his mentality is largely the resultant of his material environment Freud in the twentieth century went a step further and taught that not only is man descended from animals but his mentality retains even today traces of his animal origin

As opposed to this conception of man as a progressive animal

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1 He who knows himself knows God.

The same principle, when further developed, gives rise to the idea that man is not an isolated individual but contains in himself the entire universe In the words of the Gita (XI 7)

> *Here today behold the whole universe moving and unmoving and whatever else thou desirest to see O Gudakesa (Arjuna), all unified in My body*

A Sufi poet has expressed the same concept in the Arabic verse

> *Watahsab annaka jarmun saghir*
> *Wa fika antavi alemun akbaru* [1]

It will be readily agreed that there can be no higher concept of man God marks the highest limit of human thought By identifying man with God, the Eastern concept of man elevates him to godhead Man has therefore no other goal but to re establish his identity with God He thus becomes superior to the entire creation

II

We have till now discussed the concept of man from the point of view of the philosophies in the East and the West We now wish to review briefly what religion has to say on the question If we consider the attitude of Judaism and Christianity, we find a clear statement in the Old Testament that God created man in His own image From this it would follow that man shares in the attributes of God A strong element of spiritual mysticism has characterized the attitude of Christianity and has acted as a check to the predominance of extreme material istic tendencies

In Islam we find traces of the influence of the same outlook In fact the Koran has gone a step further in its exaltation of man The Koran proclaims that not only is man created in the image of God but is His regent on earth In speaking of the creation of Adam God says (2 29)

> *Inni jaelun fil arde khalifat* [2]

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[1] Thou thinkest that thou rt small body thou k owest n t that a uni rs gr te than the phys al w ld c tained thee

[2] I w t to e te my viceroy n rth.

This idea of the viceroyalty of man profoundly influenced the Arab philosophers Two things may be noted in this connec tion As regent of God on earth man has an immediate affinity with Him This also makes man superior to all creation and makes him master not only of animal life but also of the forces of nature itself The Koran proclaims again and again (XIII 45)

Whatever is on the earth or in the heavens has been made subject to man

It is generally recognized that Aristotle deeply influenced most of the Arab philosophers but even in their interpretation of Aristotle, they show clear indications of the influence of the idea of man s viceroyalty of God Avicenna (Ibn Sina) and Averroes (Ibn Rushd) are metaphysically Aristotelians but their spiritual orientation in Islam makes them recognize that since man shares in God s attributes there is no limit to the heights which he can attain in both knowledge and power Muslim scholastics like Al Ghazzali ar Razi ar Raghib Ispahani and others have further elaborated this idea in their various philosophical writings

We must however, admit that while the conception of man in both Vedanta and Sufism gives him a lofty status, neither of these philosophies can escape the charge that if, on the one hand they set no limit to human capacity they, on the other hand imply an element of fatalism that circumscribes man s power The explanation of this paradox is to be found in their concept of the relation of man to God Since man is an emana tion of divinity whatever man does is ultimately God s doing whatever happens is due to the will of God From this it is but another step to think of man as a mere toy in the hands of fate

It has been said that while the concepts of Vedanta and Sufism in their pure form have been responsible for some of the highest spiritual attainments of man they have to some extent acted as an impediment to human progress on the secular plane Emphasis on the unity of man with God made society relatively insensitive to human suffering as such suffering was regarded as mere illusion We find therefore that Eastern societies have often been indifferent to the removal of the causes of social malaise This explains why some modern thinkers are seeking for a formulation of the philosophy of Vedanta without its fatalism

There is a similar paradox in the Western concept of man A philosophy of materialism would, *prima facie* seem to indicate a determinist outlook on life Since the law of causality reigns throughout the material world the same law would tend to hold in the field of human action This tendency culminates in the psychological theories of the Behaviourists The Western mind however asserted itself against such a deterministic concept and exhibited an energy of spirit which has rarely been equalled and perhaps never surpassed

One of the main tasks of the present Symposium should be to examine how we can combine these two concepts which have so profoundly influenced both philosophy and religious outlook in the East and the West The Eastern conception of man s status if combined with the Western concept of progress would open out to man the possibility of infinite advance without the risks implicit in the misuse of science It may also indicate a way out of the fatalism which otherwise seems to follow from the Eastern conception of man s identity with God The Eastern conception of man s status is not only consistent with the progress of Western science but in fact offers an intelligible explanation of how scientific progress is possible If man were merely a developed animal, there would be a limit to his advancement If, however he shares in God s infinity, there can be no limit to the progress he can achieve Science can then march from triumph to triumph and solve many of the riddles which trouble man even to this day

There is a further reason why a synthesis of the Eastern and the Western concepts of man is of the greatest importance to man s future Science in itself is neutral Its discoveries can be used equally to heal and to kill It depends upon the outlook and mentality of the user whether science will be used to create a new heaven on earth or to destroy the world in a common conflagration If we think of man as only a progressive animal there is nothing to prevent his using science for furthering interests based on the passions he shares in common with animals If however we think of him as an emanation of God he can use science only for furthering God s purposes, that is the achievement of peace on earth and goodwill to all men

III

I have tried to indicate that the Eastern and Western concepts of man are in some ways complementary If the one has emphasized the intrinsic excellence of his being the other has laid stress on the progress he has achieved and can achieve through his own efforts If the one has stressed the spiritual elements in his nature the other has pointed out that spiritual excellence must also have a requisite physical basis If in spite of differences in emphasis, the Western and the Eastern concepts of man can be reconciled there is no reason why the philosophy of education in these two regions should not also be fitted into a wider philosophy of education for the world

In both the East and the West the prevalent systems of education have given rise to various paradoxes The East puts a disproportionate emphasis on individual salvation Man sought knowledge as a means to his own redemption The Eastern mode of thought with its preoccupation with individual salvation has at times paid inadequate attention to social welfare and progress In the West, on the contrary, there has been a greater emphasis on the need for social progress In fact considerations of social welfare have at times led to the growth of totalitarian societies in which the individual has been suppressed Today when East and West have been brought nearer one another through the operations of science it is necessary that the bias whether in favour of the individual or of society should be rectified and a system of education evolved which will give due regard to both individual and social values

Herein lies the importance of education in the modern world Experience has shown that education can profoundly affect the development of individuals and through individuals of societies If the individual is not an integrated personality society cannot be harmonious The function of education in the modern world is therefore to build up integrated individuals in an integrated society and the concept of both the East and the West must contribute to such development

Before I conclude there is one other problem to which I would like to draw your attention The question often arises whether education is a means or an end I would say that on the whole the West has looked upon education as a means

while the East has looked upon it as an end If education is regarded as a means, the question arises what is the end for which it is a means The West has often regarded social welfare as the end, but social welfare is a concept which can be inter preted in different ways In any case, the tendency to regard education as a means leads to some diminution in the value of education I am inclined to think that the Eastern concept shows a truer understanding of its real nature By regarding education as an end in itself we recognize knowledge to be one of the ultimate values I do not think that any Western philo sopher would deny the importance of knowledge but its value cannot be fully appreciated unless education is recognized as an end in itself Further such recognition would raise the status of man From this point of view also I am inclined to think that we should look upon education as an end rather than as a mere means to some external good

IV

To sum up In the Eastern concept, man as an emanation of God shares in His infinite attributes and is capable of achieving mastery over the entire creation In the Western concept, man is no doubt an animal but there is no limit to the progress that he can achieve in the material field His scientific achievements are visible proof of his superiority over the rest of creation and have given him domination over the sky sea and earth We may therefore say that Western practice has substantiated the claim which Eastern theory has made in respect of man Since however, the Western concept has not emphasized the spiritual origin of man his triumphs in the scientific field have themselves become a source of danger to his survival If there fore the achievements of Western science can be utilized in the Eastern spirit of man s affinity with God, science would become an instrument not of destruction but for the establishment of human prosperity, peace and progress

I hope this Symposium of philosophers from East and West will succeed in reconciling the concept of man as a spiritual entity with the concept of man as capable of infinite material progress and thus help in the realization of the Kingdom of God on earth

Address

by

H E Dr S Radhakrishnan

If a future historian is asked to describe the central feature of our age, he will not refer to the social and economic upheavals, the wars and catastrophes which fill the headlines of our newspapers but will point to the growing unity of man kind Whether we like it or not we live in one world and require to be educated to a common conception of human purpose and destiny Peace is the main objective of nations in the East and in the West Peace is not the mere absence of war it is the development of a strong fellow feeling of fraternal appreciation of other people s ideas and values Distinctions of a physical character diminish in importance as the appreciation of the significance of the inner life of man increases

It is a happy augury that this conference is organized by Unesco *which is the specialized agency of the United Nations* charged with the task of promoting mutual understanding and intellectual solidarity Here we are assembled, representatives of the East as well as of the West, to join hands in the great work of building bridges between peoples on the plane of mind and spirit There is much we have to learn from the peoples of the West and there is also a little which the West may learn from us This is possible only if we approach our task in a spirit of humility and teachableness

Our Prime Minister Jawaharlal Nehru made a confession some time ago that he was a queer mixture of East and West out of place everywhere and at home nowhere We must learn to be out of place nowhere and at home everywhere

Mankind can realize this unity only by a scrupulous appraisal of the ideas and ideals of life underlying different civilizations and by the development of a world perspective, in which the different experiments of human life fall into their

places The general impression that the whole spiritual and material background of the East is so different from that of the West that neither can ever understand the other, is wrong There are no fundamental differences in ultimate values, though there are significant differences of emphasis The fundamentals of human experience, the data for philosophical reflection are everywhere the same—the transitoriness of *things the play of chance, the emotions of love and hate* of fear and jealousy, anxiety to overcome the corruptibility of things Regarding these, there is neither East nor West The two developed appreciably similar views in regard to the nature of reality, the concept of mind and the theory of know ledge The causes which have split up the map of the world do not indicate so profound a division of mind and spirit as may be found in the members of the same family or in two citizens of the same country

The world is unified physically but is mentally divided We all live whether of the East or of the West in what has been called the contemporary uproar It is our task to produce normal balanced individuals in whom the inner and the outer life are reconciled When we reach difficult places when we face hard problems which seem formidable, we get back to first principles and raise the question of the ultimate postu lates of thought and life

II

Today, when reference is made to East West relations often we do not have in mind the Orient and the Occident Asia and Europe, but the political East and the political West of Europe When Christianity was the prevalent religion of Europe the Roman Catholic and the Protestant forms re presented the West while the Greek Church and the Russian Orthodox Church represented the East Even today in the elections to the Security Council, the seat allotted to Eastern Europe is being contested by Greece and Byelo Russia The split between the Communist East and the Democratic West is a split within the Western world

The pedigree of Communism can be traced to Plato, the New Testament, the Levellers of Cromwell s day, Ricardo, Adam Smith, Hegel, Feuerbach Marx Engels Lenin

Some of the characteristic features of Communism are those of the West

The Greek mind was of a dialectical order It laid stress on the primacy of reason Communism claims to utilize a scientific method and analysis It is possessed of a sense of certainty, a sense of its own infallibility

Humanism has been a character of Western thought from the Greek times The Greeks concerned themselves with social conditions and postulates The Marxists wish to bring about a perfect society on earth They protest against the effects on the working classes of the industrial revolution starvation wages child and female labour overcrowded slums destruction of family life In the name of social justice, they criticize the capitalist order

The logic which drives a missionary cause to aggressive propaganda is nothing new in history Go ye into all the world and preach the Gospel to every creature

The law of contradiction lays down that contradictories cannot subsist together The conflict between the Communists and the non Communists is on the same pattern as the conflict between the Jew and the Gentile the Greek and the Barbarian the Christian and the heathen, the Protestant and the Catholic This view is based on the philosophy of either or It divides the world into two opposite camps—the kingdoms of light and of darkness

We shall have heresies and persecution of heresies so long as we have a sacred doctrine and an authorized body of interpreters If dogmas are the expressions of final and infallible truth, we cannot escape from doctrinal controversies and inquisitorial methods During the early centuries of Christianity seven councils were held to define the true doctrine and pronounce against heresies

The main though not the exclusive emphasis of the West is on scientific reason humanism missionary propaganda and a division of the world into opposite camps Communism exaggerates all these features In his work on the teachings of Karl Marx (1914) Lenin writes that Marx was the genius who continued and completed the three chief ideological currents of the nineteenth century, represented respectively by the three most advanced countries of humanity classical German philosophy, classical English political economy and

French socialism combined with French revolutionary doc trines

Not only is the creed of Communism a product of Western thought but its propagation is also due to leaders who were trained in Western capitals Berlin, Paris, Geneva In the first world war it was the German High Command who put the future Russia into a railway coach, sealed it and sent it out to explode in the then Finnish station of Petrogradt[1] It is there fore somewhat strange that Communism should be treated as an Eastern doctrine though it is now spreading in the East

III

Eastern thought has been characterized by a different outlook Its main features are faith in an unseen reality of which all life is a manifestation the primacy of spiritual experience and anxiety to harmonize apparent opposites This view of life awakened a large part of Asia to thought and art and influ enced other parts of the world

The real is the essence of the soul The aim of a human being is union with reality This union is to be effected not by reason alone but by the whole personality We must grasp the real not only by thought but by our whole being It is not a question of entertaining ideas but of transforming the self renewing our being By contemplation we transform the whole man and assimilate him to the nature of the object

Religious experience is a vision, an awareness, a release into boundless freedom This awareness is what is called know ledge, its opposite is ignorance, confinement within the narrow bounds set by the mind and the senses As religion is experience of reality, there is less concern with religious doctrine than with religious feeling, religious life Religious conflicts relate to theories of the universe, to doctrines of God Religious experience is not a matter of belief in a set of propositions but response of the whole self to the daily challenge of actual human relations It is a way of living, of love and wisdom This does not depend on theories A sense of the mystery

[1] Th Brit h F reig Off ce w t n th t th B l h k w th p d ge t f Impe l Germ y d Bolsh vism was " m me t fost red sol ly f the furth an f Germ ds

of God produces humility which is a foe to all fanaticism

Refusal to transgress the limits of the definable comes out in the teachings of the Upanishads and of the Buddha The real is *advaita*, non dual *advitiya*, secondless The Buddha who preached wisdom and compassion did not indulge in theories of reality

The Tao that can be expressed is not the eternal Tao, the name that can be defined is not the unchanging name

Doctrines are necessary, we cannot think what we like But they are all inadequate we cannot enclose the truth within words and concepts The language in which the truth is expressed consists of many dialects adapted to the needs of different peoples

If conformity to doctrines is to be regarded as the final test believers in different creeds will be profoundly alien to one another If modes of life are taken into account religious men can be said to be like one another The view that our creed represents the truth and those who deny or dispute it are heretics is a dangerous one India has been the home of different religions and the Indian attitude has been one of hospitality to other creeds In consistency with this spirit the Indian National Congress passed a resolution on 19 October 1951 in the following words It has been the aim and declared policy of the Congress since its inception to establish a secular democratic State which while honouring every faith does not discriminate against any religion

Dr Karl Ludwig Reichelt in *Religion in Chinese Garment* says "The Chinese are at the same time Confucianists Taoists and Buddhists This is given visible expression not only in the circumstance that some of the divinities are to be found in all the religious systems but also by the fact that in some of the smaller localities there are common temples where the respective God images of the three religions are enthroned in full harmony While the daily worship is connected with the ancestral tablets of the home, the average Chinese likes to visit some temple on special occasions and whether it is Taoist or Buddhist makes no great difference If you press him and question him more particularly about his philosophy of life as a whole you are apt to hear many curious things most often a loosely articulated system of thought in which the old Chinese outlook, shaped according to Confucian pattern

has been loosely combined with a Buddhist philosophy of existence [1]

This concept of man stresses the spiritual as the principal element as distinct from the rational Every individual has a spark of the divine He is essentially subject not object If we attempt to possess him as flesh as mind to be moulded, we fail to recognize the essentially unseizable Man is not a product of natural necessity as he bears the image and impress of the divine

While the unique value of the human individual is admitted theoretically its implications have not been worked out in the social structure There is more real democracy in the West than in the East That many men should, by the accidents of birth and opportunity have a life of toil and pain, hardness and distress while others no more deserving have a life of ease, pleasure and privilege arouses indignation in sensitive minds

Because of the latent divinity of all men, no individual, however criminal he may be, is beyond redemption There is no such thing as all hope abandon ye who enter here The spirit is in each one as a part of himself as a part of the sub stratum of his being It may be buried in some like a hidden treasure beneath a barren debris of brutality and violence but it is there all the same operative and alive The light that lighteth every man that cometh into the world' cannot be put out Asanga tells us to have compassion for the wretched compassion for the hot tempered, compassion for the angry compassion for the slave of passion, compassion for him who is obstinate in error Santideva asks us to do good even to our worst enemies Honen, the Japanese teacher (1133-1212) taught the worship of Amitabha Infinite Light There is no hamlet so forlorn that the rays of the silver moon fail to reach it, nor is there any man who, by opening wide the windows of his thought cannot perceive divine truth and take it unto his heart

These are the central principles of the Christian religion, whose heart is that of the East, whose brain—its theology, whose body—its organization, are Graeco Roman Jesus emphasizes the central simplicities of all religion Thou shalt love the Lord thy God, Thou shalt love thy neighbour as

[1] E.T (95) p 173

thyself We are called upon to develop the mind that was in Christ Jesus The way and the truth are to end in life Again "The Kingdom of God is within you St Thomas Aquinas says Great is the blindness and exceeding the folly of many souls that are ever seeking God, and frequently desiring God, whilst all the time, they are themselves the tabernacles of the living God, since their soul is the seat of God in which He continuously reposes God is nearer to us than we are to our selves St Augustine says When there is a question whether a man is good one does not ask what he believes or what he hopes, but what he loves In my Father s house are many mansions

Jesus asks us to love our enemies The doctrine of eternal hell is inconsistent with the spirit of Jesus teaching Father, forgive them for they know not what they do ' 'For He maketh His sun to shine upon the evil and upon the good and sendeth His rain upon the just and upon the unjust. ' The Psalmist says If I ascend up into heaven Thou art there, If I make my bed in hell, behold Thou art there also " If we do not see God everywhere we see Him nowhere The end of the world is the transubstantiation of all creation the universal incarnation

Dr Walzer asserts about Al Farabi s views There is one universal religion but many forms of symbolic representation of ultimate truth, that may differ from land to land and from nation to nation they vary in language in law and in custom, in the use of symbols and similitudes There exists only one true God for the philosophical mind but He has different names in different religions

IV

In a world filled with anger and hate where we look in vain for a smile of humanity for a sigh of understanding we must turn back to that fundamental religion of spirit which is neither Eastern nor Western but universal if we are to bring to our task a little hope a little charity Except the Lord build the house they labour in vain who build it " Unless we have a sound attitude of mind a spiritual philosophy of life we cannot build anything that will endure We must adopt the Eastern outlook on life with its faith in the divine possibilities of the human soul unity of all life and existence

and insistence on an active reconciliation of different faiths and cultures so as to promote the unity of mankind

Man, as the object of scientific enquiry as fully understand able in terms of race, or heredity psycho analysis or economic determinism is neither the true nor the entire human being He has in him the element of spirit which gives him his uniqueness No man is the duplicate of his neighbour, no one is a mere example of a class He is more than the rational historical being He is a vehicle of the divine From the spirit in man his powers and qualities fan out like the spokes of a wheel to the rim which is his outward form The closer any thought or action approaches to the centre the greater is its intensity and the more closely is the diversity integrated into unity The farther it is from the centre, the wider is its exten sion and the looser its integration

We should look upon apparently conflicting opposites as not fundamentally incompatible but as capable of reconciliation by mutual modification if necessary There are two ways of dealing with evil and error the way of firm resistance a steady denial negation, the other is the way of comprehension which enters into the mind of the erring or evil individual and transforms him from within Psychological conflict as much as physical warfare darkens the mind both of those who use it and those against whom it is used The whole history of Western development as of any other cultural growth illus trates how different currents have mingled their waters Even the so called heresies which were condemned and persecuted have become part of the Western heritage Though Justinian closed the schools of Athens and did not desire any compromise with neo-Platonism the latter entered into the stream of Christian thought St Augustine s deepest ideas on God and the world were moulded by neo Platonism In the Middle Ages, heretical and non Christian Aristotelianism influenced Christian theology St Thomas Aquinas used the foundations of Aristotle for building his revealed theology Gibbon saw in the history of the Crusades the world s debate and yet the spirit of Islam has influenced the world s thought Look at the devastating wars between the rival fanaticisms of Catholicism and Protestantism three centuries back Their seemingly insoluble conflict has now faded away

All this teaches us that our enemies are not as black as we

paint them when our passions are aroused Five years ago we hated the Germans and the Japanese We vowed a Carthaginian peace We were forbidden to speak even to their children Now we are on the Rhine as guarantors and friends of the Germans We have concluded a treaty with Japan We are now prepared to welcome these dangerous' people into the family of free nations and harness their dynamic energy for democracy Suppose we win the next war for which we are making such vast preparations, are we sure that we will not be in the same predicament again with a change of partners?[1] History warns us that the present conflict between Marxist logic and missionary fervour on the one side and our zeal for God and man on the other, can also be terminated by a process of understanding and adjustment If we know only our side of the case we do not know even that Need we revert to the ancient pattern of self righteousness dividing mankind into sheep and goats Charity is the quality we need most St Paul s statement that we are members one of another is a true observation as well as a call to moral order If we wish to achieve peace we should avoid the passion of self righteousness which gives to every conflict a religious flavour When a war is of ideologies we resolve to win the war even if in the process the whole world is ruined When we fight for a piece of territory the war will cease when the objective is achieved If we fight for righteousness, we are dedicated to a war of destruction The military methods involved in a new war are so disastrously dangerous and the economic social and cultural consequences of a third world war would be so catastrophic that the winner would be left with nothing but uninhabitable ruins and unalterable misery Any man in his normal state of mind will shudder at the prospect We must save mankind from collective suicide

Mankind is once again standing on the brink of an abyss the depth of which no man can presume to measure. There is a new sense of foreboding a sense of fatality of vast masses moving slowly and irresistibly towards a final collision Let us dedicate our gifts to a reasonable objectivity and sanity in our

[1] We might even say that if the whole of Russia and the entire body of her satellites were to be buried under the deepest ocean from that moment something like the same predicament would still be with us tomorrow though the terms of it would be transposed by a regrouping of the remaining powers H bert B rő ld *The Scen fic b rom the Moralistic Approach to International A* Int rn tional Affairs (Octobe 95 p. 4 4)

thinking Neither the political East nor the political West need imagine that they are the appointed educators of humanity It is our task as thinkers above the battle, to act as bridges—when all the bridges are down—not only between East and West but also between the partial and complementary truths buried under the warring philosophies The spirit of religion is the essence of democracy Appreciation of differences is a characteristic of both Democracy functions where people differ and not where they agree

When the Soviet leaders speak of the coexistence of the two systems, they get behind their doctrinairism and adopt a view which brings them close to Eastern thought In a lecture to Communist leaders Stalin once said If capitalism could adapt its production not to getting maximum profits but to the systematic improvement of the masses of the people then there would not be any crisis, but then capitalism would not be capitalism *We need not quarrel with words America,* prominent among capitalist countries is striving to improve the general welfare, not only of the Americans but of the whole world With the lessening of the general tension, the Soviet system itself may undergo radical changes and become a true people s democracy where there will be the freedoms whose lack in Russia we deplore

The Greek and the barbarian the Jew and the Gentile the Christian and the Moslem, the Protestant and the Catholic, the Allies and the Axis powers of the last war have now learnt to live together It is a matter of no small importance for the peace and advancement of the world that the Communist and the non Communist should learn to live in this world, if not in harmony at least in reasonable mutual accommodation Even in a family, if the husband and the wife cannot love each other they learn to put up with each other If we put up with people it does not mean that we give in to people If we have a little more charity, the possibilities of the future seem to be infinite surpassing all hitherto known forms of adventure

In this troubled age the responsibility, nay the opportunity, of the leaders of thought is great for in the long run, ideas, not things, will determine the future of mankind We have for our motto an ancient text which proclaims that truth will conquer The spirit of man will prevail the spirit capable of under standing, endurance and compassion

Essays written by the Participants in the Round Table

Some Aspects of the Relations between East and West

by

ALBERT BÉGUIN

GENERALIZATION of the vast question suggested as the subject for our discussion would be impossible without dangerous simplification I shall therefore confine myself in the present instance to comments *on facets* of the problem which can serve to initiate a discussion

THE AGE OF CIVILIZATION

When we compare Eastern and Western man on the basis of the most widely accepted definition of each the date of the composite images we use is either the present or the relatively recent past. In other words we are taking the two types of man (or civilization) either as they are today in the twentieth century or as they found each other in a period which may be taken as coinciding more or less with the Renaissance (contacts particularly by the Arab world were numerous and fruitful in the Middle Ages but it was a period at which appreciation of the differences between cultural "families lacked all precision interest in the exotic was limited and means of research still primitive) Granted that the essentially traditionalist temperament of the East tends to produce a kind of static condition (to which the East ascribes the fortunate persistence of certain fundamental values but which the Occidental tends to regard as being to some extent stagnation) it may be argued that the Eastern world is ageless or at least a world whose ideal it is to remain unchanged by time The Occidental on the contrary has long been conscious that his is a world in movement and he is prone to equate its changes with progress When he first came in contact with the civilizations of Asia the impression made on him was that he

had advanced beyond them and that they were at a stage of evolution which he had passed

This Western view is of course far from unchallengeable at any rate so far as it implies a value judgment It must never theless be taken into account, for instance when it is suggested that the specific feature characterizing the Western mind and distinguishing it from the Eastern cast of thought is its distinc tion between the sacred and the profane the spiritual and the political or when it is claimed that the dominant tendency of the West is purely one towards scientific knowledge, mastery over the physical world and personal liberty All this is appli cable (but only to a very limited extent) to the modern civili zation of the West, though it would be but the crudest carica ture of the Middle Ages All the characteristics accepted as most typical of the Eastern plan of life—the primacy of the spiritual the daily contact with sacred things the emphasis on the interior life and the ideal of sanctity—are as typical of medieval Europe

It is therefore not surprising that the rationalist thought of the past two centuries should have concluded, from these facts that the West had attained a stage in terms of absolute progress behind which Asia lingered, firmly caught in a past age of history For those who accept this view it is an easy step to the hypothesis of a necessary evolution of the Asiatic peoples destined to pass through the same stages along the same way as ourselves and hence aided by our influence This point of view often had a powerful hold on the minds of European laymen and missionaries overseas and when, as in Japan, examples began to occur of rapid assimilation of technology and when to cap it its concomitant proved to be the birth of nationalism in Asia this was regarded as a confirmation of the progressive hypothesis

In its pristine form this hypothesis is no longer tenable—at a moment when the greatest crisis of all time appears to be the price paid for a line of evolution which it is difficult to continue calling progress The West is being led to revise its scale of values and to reconsider the work of its hands and mind There are some who seek a yardstick for this examination of conscience and amendment of life in Europe s oldest heri tage, the legacy of the Christian Middle Ages Others as yet few in number, turn to the wisdom of Asia—not always

drawn admittedly from its clearest fountains However, very many remain faithful to the European concept of historical evolution to the extent of maintaining that the solution lies ahead of us, in perfecting, not in resisting, mechanized civilization (the Marxists are not alone in thus turning their faces to a future seen as the crown of the work begun in the West with the Renaissance)

Whatever the truth may be, we must not reject without further consideration either the notion that there is a scale of relative ages of civilizations nor the hypothesis that the peoples of Asia have started along the road on which Europe has preceded them However, in the light of the present crisis, we cannot assert with confidence that evolution on these lines might not lead to death instead of life We should view both the relative ages of civilizations and the differing genius of the peoples with other eyes not as destined in the course of years to be reduced to the dead level of a civilization truly world embracing (or at least more nearly so than now) but as the elements in a blessed diversity and to see in the differences arising from the diversity of age and genius so many special and necessary vocations The right solutions for our problems would no longer be deemed to lie in the triumph of one civilization over another of which it was the guide and teacher they would follow from the sharing of the treasures of which each was the guardian The immutability of the East would be given its true value as a cherished treasure of spirituality needed by a world riddled with activism On the other side the urge to tame the earth on which we live would be recognized as a useful complement to a too passive spirituality

This attitude seems to me the only one which justifies an attempt at rapprochement and interchange between East and West

THE MEANING OF HISTORY

One of the outstanding acquisitions of Western thought is the philosophy of history Ever since Hegel Liberal and Marxist thought alike have assessed the significance of human life in terms of an historical process whose laws they seek to determine

This notion of the march of time as having significance—even a mandatory significance—would appear to be foreign to the East However, it is not foreign to the traditional spiritual ity of Europe It was the attempt to develop a theology of history (St Augustine) which distinguished medieval Chris tianity among other things from the religious and mystical thought of the East, and the reaction of Christianity in our own day to the modern materialist philosophies has been to seek to revive that great tradition Hence the return to a long neglected eschatology which re emerges alike in the neo Calvinism of Barth and in Catholic theology and even liturgy, as in the restored waiting Liturgy of Holy Saturday The world is viewed in the perspective of Judgment Day and the whole time process, and all the involvements of each of us in it, are thereby seen to scale (that is the significance, more particularly of the work of such thinkers as Peguy and Claudel) It is this outlook which has given rise to the new schools of Christian thought these pay close attention to contemporary history and take the view that the created being does not work out his salvation by himself but in the community and as a member of it

This is the most considerable modern attempt to relate life in time to a spiritual background and may be the first step towards a synthesis which the East could grasp on the basis of the primacy of the spiritual and which the agnostic West could understand from the starting point of the natural brotherhood of man and the demands society may make upon the individual Given this hypothesis, a great importance would undoubtedly be given to the differential appreciation of the ages of civilizations, of the genius of the various nations and of their contribution to the solution of the crises of today provided, however that the concept of the time process as a steady linear progression was replaced by the more complex notion of a number of coexistent time progress regimens—that applying to intellectual and scientific knowledge which is the most linear of all that of historical events shrouded in the obscurity of incomprehensibility, that relating to the conquest of tyrannies of every kind in which progress is by bursts fol lowed by relapse and a new beginning, and that of spiritual growth, which is perhaps a regimen of lapse of time with no progress bound up with tradition (according to the East)

linked with the salvation of the individual (according to Christianity)

The concept of the multiplicity of time regimens is the com plement of that of the multiplicity of types of national genius and removes the dangers that lurk in the idolatry of history (Marxism)

SOCIAL CRISES

In one respect at least the position of East and West is very similar In both worlds re examination of the traditional forms of civilization is demanded by the conditions of material, intellectual and moral destitution in which a considerable majority of the world s present population exists There has always been widespread destitution among mankind (Middle Ages crises in Chinese history, etc) but the growth of the world s population, coupled with the new types of altruism evolved by modern thought have made the inequality of living standards a yet more crying scandal In Europe the prevalence of injustice and oppression is a fact which none would dare to deny, American prosperity hides open sores over vast regions of Asia men live a sub human life of which the very thought is intolerable to men of conscience In the face of this appalling evidence it is all too clear that the schemes of values on which our several societies have long been founded no longer suffice for the attainment of viable solutions We must re examine them from the ground up

More particularly education requires to be entirely recast in the light of two facts the present numbers of mankind and the hopelessness for many of them of ever having access to culture in the traditional sense Neither in Asia nor in the West can there be any further question of forming an abstract judgment of the value of a particular concept of man or of a particular educational ideal Both must be thought out afresh in terms of the circumstances of the majority of our kind Marxism has made the attempt from its own angle We must now see whether we are able to proffer answers other than the Marxist if we cannot, we are finished

WORK

It is a matter of special urgency to consider the meaning of human labour in terms of our respective countries and civilizations and under the threat of permanent crisis The problem has always existed theology and philosophy have met it but their answers seem always to have been given on the basis of particular social and economic conditions (slavery in antiquity or more modern times—the Negroes—servile status of manual workers and glorification of certain activities regarded as noble, etc)

The initial tendency of a rapidly growing technology was to ease the lot of man and in practice it did bring about indisputable progress in this respect with work made lighter hygiene improved and machines replacing manual toil There is no need to set out in detail the other side of the picture, in which technical progress figures as the source of such grave evils as the subjection of man to the tyranny of cold statistics his reduction to a nameless unit, the loss of the creative element in work and of independence Moreover there is the darker aspect of the application of modern resources to war and destruction, and the risk of power being concentrated in the hands of the few and ultimately in those of inhuman and irresponsible entities (States financial combines dictators)

Some people who claim to follow but who perhaps over-simplify the lessons of Asia would be inclined to pronounce technology to be evil in itself, the accursed offspring of human pride and of a spirit of domination which would bend Nature to its unholy purpose To them the only remedy is retreat into the past, the destruction of all machinery and man s return to solitude and meditation But this is vain nostalgia, history does not retrace its steps and the men we have to save are not men of yesterday but of today with all they have and lack now with their present convictions and yearnings Technology and science are instruments and, as such, are neither good nor bad They must be not destroyed but tamed and restored to their proper status They are dangerous when they become idols, but when they are kept in their place as instruments only, the danger vanishes Thus a great spiritual renaissance will be needed to restore them to their true focus

The initial effort—and this has enormous implications

educationally—must be concentrated on creating what now is almost entirely lacking a spiritual background to work The traditional Christian background is still conceived of in terms of outmoded forms of human toil, while the Marxist version remains marked by nineteenth century materialism and by a messianic spirit of revolution which is extremely potent during the period of struggle against tyranny but does not furnish a valid ethic for a new society

Here again the East, with its notion of man s fellowship with the rest of the created cosmos, could make an important con tribution to the building of an ethic of work in which other elements would be the Western regard for fair shares and a satisfying efficiency

EDUCATION

From all the foregoing there should emerge the main lines not of an educational system but of a policy for education The crisis in which we are living compels rejection of the aristocra tic systems through which other civilizations produced minori ties of outstanding culture, while leaving the people as a whole in its ignorance Whether we like it or not the spiri tuality of the masses is no longer vital enough to replace all other knowledge The very fact of their being reduced to such grim straits has brought the masses of today not indeed to maturity for they are not themselves capable of ensuring their own material and spiritual progress but to a stage in adulthood at which they realize more and more clearly their right to culture Western societies (including America) have long met this claim by allowing the underprivileged the crumbs—or a faint reflection—of the culture imparted to the few This has involved no change in the principles of what is still called "humanism but is perhaps merely the education appropriate for the men of an age now past The schools still purvey learn ing only remotely related to life as our contemporaries know it Where the syllabus is modernized the process consists in the inclusion of science or, more accurately applied science—that is an education that breeds mere technologists if not slaves of technology, it will never humanize technology, master it, spiritualize it in modern terms for it is created for and by

technology, with never a window on the outer world Even the educational media which technology has invented—radio, films etc —only complete in the adult what has already been begun and carried far in the schools

While the writer claims no special knowledge of Asia, it may be asserted that the majority of Eastern peoples have not reached the stage described above Among them the educa tional problem arising is that simplest type, long since resolved in Europe, which consists in conquering illiteracy, and the great danger lies in the fact that the masses of the East are catapulted into a world dominated by technology without a transitional stage and without its being feasible to give them in short order the knowledge which would enable them to form judgments on it and to escape in some measure the domination of their intellects by technology We may, how ever reckon with equal justice that some surprises may be expected from this encounter of peoples emerging direct from an age of faith with the assumptions of technological civiliza tion At the very least, we must not fail to note the effects of this encounter on a still living spirituality which has not been degraded to the level of a mere science

Thus in East and West alike completely dissimilar and al most opposite circumstances create the danger of man s subjection to the impersonal tyranny of figures, technology and material success What we have to find are the reserves of spirituality respect for human personality and the sense of what is sacred in all civilizations and all tradition which could serve to fashion a new type of man, a man who takes full advantage of the instruments he has invented but with a renewed awareness that he is capable of greater things than the mere mastery of nature

Any education whose effect is not to promote this reawaken ing is a sure way to the tyranny of man over man No method of education, however scholarly and however soundly based on tests and statistics, is beneficial in itself Our analytical knowledge of man has, of course, resulted in educational, as in medical, progress but all it has done has been to improve the technique in either case It is not thus that the mind is enriched and there are no methods for attaining the true liberty to which all men aspire The source to which men must return is man himself

But it is not one source but many, each differing according to an epoch and tradition We shall make no progress by formulating and agreeing on a single definition of man in the abstract The diversity of mankind the very richness of this diversity might be compared to the music of the symphony to whose complexity each instrument contributes its note

Humanistic Education in the West

by

JOHN T CHRISTIE

I am asked to contribute a point of view on the subject of our forthcoming Conference, and a point of view especially on educational questions, must be coloured by a man s own educational background and limitations Speaking as one who had an old fashioned classical training at school and college, I have returned after nearly 20 years as a head master, to be the principal of an Oxford college I am very conscious that Oxford like other less ancient universities has changed its outlook It now stands for a wider and more democratic view of education and secondly the study of science has increased enormously in range and importance

However although a classical education may not be the one best calculated to fit a man for the immediate problems of 1951 it should enable one to understand the history of cul ture and education better than a scientific outlook can In fact all humane education in Europe since the Renaissance and particularly in the nineteenth century was strongly influenced by a classical outlook It has often been claimed that it is the foundation of Western civilization and I have frequently seen the phrase Western or Christian civilization The two epithets have very different implications as we shall see My knowledge of Eastern thought is small and superficial it is a compound of interest tending towards admiration, tempered by ignorance tending towards wonder The view of the ordinary Englishman who has a similar background to mine is that the Eastern ideal is contemplative and tends towards the negation of self, while the Western outlook is more practical and more self conscious At first sight one might expect a knowledge of the humanities and a humanistic education to be the ideal bridge between the two and it is worth enquiring how far this is a right view If it were it

would greatly help us to answer the question which is to be discussed at this Conference

A training in the humanities and a training in science share between them the school and college education of English men today, and evidently the humanities are nearer to Eastern philosophy than science is Nevertheless from the first, hu mane ideals inculcated by training in literature and art and religious observance, have been strongly coloured by the practi cal bent of the Western mind and the classical emphasis on conscious reason and a sense of form All this of course took its rise from ancient Greece, and in the writings of the Greeks there is little of the contemplative ideal, though we can find traces of it in Plato Here as elsewhere Plato is too great a man to be entirely typical of his nation and his age Even to him poets were teachers and prose writers were persuaders active reason and not passive meditation is the master con ception It is noticeable that recent left wing students of the ancient Greek outlook tend to criticize Greece and the classical education founded on it for not being practical enough and for a failure to develop science in the interests of society as a whole A number of recent writers have attacked all that is mystical and religious in Greek literature and in so doing have exaggerated this element

Christianity the second strand in our Western tradition no doubt had a strong strain of contemplation in it and still has But it was quickly Europeanized by Greek reason to fit it for its conflicts with a pagan world The mere fact of the use of the Greek language strengthened this tendency, and soon it became yet more organized and practical in its outlook when it became the official religion of the Roman Empire The Renaissance only stressed anew the debt of Europe to the classical outlook and perpetuated the aristocratic aspect of classical education a fact which both limited and strengthened its effect Classics, especially in England were the foundation of the ruling class outlook and one can see even today that politicians brought up in this tradition feel themselves more at ease with imperial and foreign problems than with domestic and economic questions which have no parallel in the history which they had studied Western culture in the usual sense was never more than the culture of a small minority Among our thinkers and writers in England in the last two centuries

there have always been a few whose interests were directed to the East often beginning with our political and economic connexions But I imagine that they were always isolated and somewhat alien figures Such an interest and such a point of view only became popular when it was absurdly romanticized and distorted by the poet and even by the lady novelist The second half of the nineteenth century was the time of our greatest material prosperity, and it was characteristic of the Western qualities of enterprise and individual initiative But that period bred its own critics and Matthew Arnold gives a memorable though perhaps idealist picture of the Eastern character as it seemed to us in one of his poems, which is worth quoting

In cities should we English lie
Where cries are rising ever new
And men's incessant stream goes by—
We who pursue

Our business with unslackening stride
Traverse in troops with care fill'd breast
The soft Mediterranean side
The Nile the East

And see all sights from pole to pole
And glance and nod and bustle by
And never once possess our soul
Before we die

Some sage to whom the world was dead
And men were specks and life a play
Who made the roots of trees his bed
And once a day

With staff and gourd his way did bend
To villages and homes of man,
For food to keep him till he end
His mortal span

And the pure goal of being reach
Hoar headed wrinkled clad in white
Without companion without speech
By day and night

Pondering God s mysteries untold
And tranquil as the glacier snows
He by those Indian mountains old
Might well repose

Since Matthew Arnold a great change has come over education and it certainly has not been a change in the direction of Eastern philosophy Science puts an equal emphasis on form and on practical results, and also, quite unlike the humanities it stresses what can be weighed and numbered and is reducible to statistics Thus it would appear to be further than ever from the traditional Eastern outlook But it is worth remembering that even so, science is a great internationalizer (I well remember a Unesco conference in 1946 in London attended by Professor Gilbert Murray, Dr Julian Huxley and the President of the Royal Society We heard an eloquent plea from a politician for more interchange of ideas between East and West and for the encouragement of Unesco Eminent speakers at once pointed out that their own departments science mathematics philosophy already had strong links of this kind and it was obvious that the scientists, in their own subject, inherited a great common tradition, the equivalent today of the seventeenth century ideal of the republic of letters)

Even so it seems that neither science nor the humanities by themselves can be the foundation for a bridge between East and West Clearly if the unity of knowledge and the unity of the world is to be saved in this precarious century we must do our best to bridge the gap On our side I doubt whether this can be done by trying to infuse an oriental element into our education Certainly at the schoolboy stage and here I speak from some experience the Eastern outlook as given in books that are intelligible to immature minds seems hard to grasp I have more than once used with a class of clever boys of 17 to 18 a book about Eastern religions They could understand what was written but found it hard to link it on to anything with which they naturally sympathized They are told for instance that in the Eastern world view there is no such thing as individuality persons are no more individual than the waves of the sea have a separate entity as waves" I remember being asked to explain what was meant and I found myself quite unable to do so Perhaps we shall hear more at this

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And the pure goal of being reach
Hoar headed wrinkled, clad in white,
Without companion without speech
By day and night

Christian tinge Indeed, the typical Englishman of the nine teenth century, especially if he was of the kind who came out to India, took the ideal of the gentleman as his guide and made his Christianity depend upon it You may have heard the story of the British officer who was captured by Muslims and offered his life if he would renounce his Christianity He had never noticeably been a Christian but he refused to abjure his formal faith because it was a damned ungentle manly thing to do [1] (Is it true that a similar change has come over Buddhism in the Far East? I have seen it stated that after Buddhism had reached China it was stiffened with Confucian ideals rather as our Christianity was stiffened with stoicism) No doubt this contemplative element needs to be made more practical or combined with a practical life if it is to stand up to modern demands but there remains the danger that it may be swamped by the typically Western materialist approach We in the West appreciate the power and the wisdom of some Eastern ideals and we should try to introduce such ways into our own education both at home and at school But I am not sure from what I have heard of present Indian education that this aspect of education is stressed any more here in India than it is with us, in fact it may be less emphasized (I should like information on the point) Is it true that Indian universities are at the mercy of examinations even more than our own universities, and do not take as their ideal knowledge for its own sake? I am sure that we in England suffer from the tempta tion to regard our universities as means to an end degree getting machines I need only refer to Sir Walter Moberley s book *The Crisis in the Universities* If the East has copied this side of Western education I am afraid it has copied the worst

We have our own university problems some of them peculiar to this age, and I do not know how far they are shared by Indian universities Since I was a student myself the university is open to a vastly larger proportion of the population This is particularly true of Oxford and Cam bridge which still enjoy perhaps unfairly a greater prestige than any others There are some twenty colleges in Oxford and in a single college a hundred applications for twelve places is not uncommon This is a healthy tendency and nowadays the idler with social ambitions is comparatively

unknown at Oxford but it is a tendency with its own dangers It is my duty to interview all our applicants, and I am left wondering how far an ancient residential university is the best thing for *all* the young men (and, I imagine, the young women) who apply One feels that some are not suited by intellect or by temperament to a university career, and at the age of 20 would be better in practical work A half way house between a theoretical course of study and earning a livelihood is a technical college and most of us are agreed that England is very much behind with technical education, certainly as compared to America Again even those who are suited to further study until they are 22 or older owing to the incidence of military service have worked so hard as boys and so narrowly in order to gain an award that they are devitalized when they arrive and are not sufficiently resilient to make the most of what is offered them One excellent result of generous State aid is that the poor boy now has a good chance of reaching Oxford or Cambridge without having to face the severe competition necessary to gain a scholarship offered by the college Having seen more of other universities both in England and in America in the last two years, I am struck by the peculiar advantages of a residential university Much of what is most valuable in education goes on outside the class room and the library and takes place in the students rooms in informal groups and discussions conducted often with great vehemence and considerable ignorance but very broadening in their effects The financial problems of a residential university are great, but even where there cannot be residence, opportunities for informal discussions or debate are of the essence of a good university

There remains a second question which goes back to the very foundations of a university What is its function in the life and education of a country? There is no doubt that instruction is far more highly organized than it used to be, and no one can regret that this is so But this only increases the danger that the university may come to be regarded as a superior high school Here, I think some knowledge of the history and origins of universities is important and I find that scientific students in particular have no interest whatever in the origins of a university A university originated in a band of students who collected together to pursue knowledge for its

own sake under the guidance of some eminent personality This was the case for example at Paris and at Padua There is a sense in which a university could remain true to its origins and its functions if there were no junior students at all I must not pursue this idea at the moment, but I have heard it said that Eastern students in particular are not interested in the history of anything An abstract and unworldly outlook on life and a fundamental pessimism about progress discourages one from interest in history whereas we have learned to believe that unless you know how a thing developed you cannot understand what it is I would freely admit that our own former belief in progress had been severely shaken over the last 50 years, but this does not debar one from a sincere interest in history and origins Is it true that there are few records of any kind for the history of ancient India and chronicles have to be invented without the help of dates? We inherited the historical approach from at least two sides From the Greeks and Romans who were proud of their traditions, and scientific in their approach to chronology and from the Hebrews for whom God was essentially a god who worked through history that had a beginning and will have an end Is this sense of history I suggest in all humility a thing that the East could profitably imitate from the West? It seems to us that human beings will naturally take some interest in the past which has made them what they are and if there is no real recorded past they will invent one often to their credit

On the other hand the ideal of knowledge for its own sake in the sense of philosophical or religious knowledge is one which the East has traditionally cherished more than the West and Western thinkers could well "go to school to the sages of the East This emphasis on the world of knowledge and philosophy can never be an item in an educational curriculum It is more an aspect of the whole approach to learning and it begins before the university and even before the school

I can never forget in my own educational experience that the boys and the young men who come to the schools and universities are largely what the homes make them The home it has been said, is the first local education authority For centuries in England the home was the first teacher and schools could rely on the homes for a background of simple

and traditional knowledge in the form of tales or prayers 'This story shall the goodman teach his son , etc Schools have varying effects on the pupils and a school with a strong character leaves its stamp on all its members But unless there is some synthesis between school and home there will be a conflict The young creature will have two standards this is natural enough at 16 and such a tension is an important part of growing up But to have two standards at 26 is wrong and is an impediment to forming an integrated character I find this question acute in the personal lives of some of the under graduates I know today The doors of Oxford are open to a far wider class of student boys from simple, uncultivated and often philistine homes come suddenly into a world of older culture Many of the young men, it seems adjust themselves admirably Their parents are proud of them and they are not ashamed of their parents This is not always the case and the conflict may lead to a suspicion of education in the hearts of the parents and a contempt for a simple home on the part of the young man The only solution from our side is continued friendliness and sympathy with boys from widely different backgrounds, without a lowering of any of our intellectual standards The spread of democracy in England has made this problem acute Is there possibly a parallel problem in India and other Eastern countries where the sudden impact of Western education and Western materialism has produced a similar conflict? Is it possible that students who talk faultless English who know Milton and Macaulay by heart will return home to a way of living which Milton and Macaulay could hardly have approved? If this is so these students may be fine flowers of culture but they are so to speak cut flowers, flowers in a vase with no root from which to perpetuate in their own families the education and outlook they have learned This is an inevitable danger unless culture in its wider sense passes through the universities to the homes of the next generation

These considerations would suggest that a bridge of some kind there must be between East and West, but for the present it must remain a *bridge* across a wide and inevitable stream The civilizations on either bank of this stream go back too far to produce any true mixture of cultures In constructing such a bridge or in strengthening any bridges that we have education

must be a prime factor The purpose of such education will not be to inculcate one side with the sentiments of the *other in such a way as to shake one s loyalty to one s own* traditions but it must inculcate sympathy with a point of view which at first is bound to appear very different and in some respects unattractive It must not consist of imitation on a superficial level On our side the organized aspect of our education is not the one of which we are most proud It must be remembered that our educational machinery is only beginning to grapple with problems which have arisen from the great social revolution which has happened in England in the last 30 years We are still making progress by trial and error But behind our organization is a genuine ideal the ideal of a Western culture based on Christian classical foundations and historical in its approach This we believe is more worth exporting, not for direct imitation but for sympathetic study, and we can gain much from the converse process It means that there must be contact not only at a student level or a school level but at the level of the instinctive, unanalysed community point of view

The Concept of Man and the Philosophy of Education in the East and the West

by

Ras Vihary Das

It is not my purpose here to criticize the basic document, but I shall perhaps be able to develop my own position better by indicating my disagreement with some of its apparent assumptions It seems to be assumed that there is one civilization in the East and quite a different one in the West resulting in seeds of conflict between peoples of the different regions, and that by mutual understanding the chances of conflict may be removed or minimized As is admitted in the document itself there is not just one civilization in the East There are many, and we may altogether fail to discover any unity among them So the distinction of civilization into Eastern and Western seems almost meaningless Secondly, I would seriously question whether conflict between one people and another ever arises from any conflicting viewpoints in their respective civilizations England and France or France and Germany may be said to share the same civilization and yet there have been frequent conflicts between them I am definitely of the opinion that conflicts between nations or individuals generally arise not out of viewpoints in their civilization but from uncivilized elements in their character

Following the ordinary usage, I have spoken above of different civilizations but the question may well be raised whether it is at all significant to speak of many different civilizations Civilization after all pertains to human beings, not to material things, and men are civilized or uncivilized in virtue of certain qualities of their heart and soul Civilization thus connotes some mental and spiritual excellence, just as health means a certain physical or bodily excellence Health does not mean one thing for an American and another for an Indian (in that case medical science would be impossible), similarly civilization should mean, essentially and ideally, one and the same

thing for all The so called different civilizations mean either the different stages in our approximation to the ideal of civilization or else the different expressions or outward modes which civilization has found for itself in different circumstances

When we speak of the civilization of a country we are apt to suppose that all the people of the country are civilized more or less in the same way, but really the different individuals of the same country are not civilized in the same way or to the same extent A civilized Indian will not differ essentially from a civilized Englishman, although they may dress or speak differently, but internally they will differ widely from their relatively uncivilized compatriots to whom they may conform in their dress and speech

If it is true that all conflicts proceed from the uncivilized parts of our nature, then what is needed for harmony and peace is not merely an understanding of our so called different civilizations, but an earnest effort to civilize ourselves by disciplining our mind and will We do wrong not because our vision is blurred but because our will is vicious Nevertheless an understanding of the nature of man, not merely in his historic actuality but also and specially, in his non historic, spiritual ideality should be of immense help in all our conscious efforts at changing or improving his present unhappy condition

If we want to know what a man is, we must know what he does What he does as a man, i e rationally always implies some ideal which he seeks to realize in or by his acts If a man s life cannot be separated from his acts we must admit that his ideals form an integral part of his nature The ideal of a man s life is the god he actually worships It is this god which shapes a man s life after its own image Any other god unrelated with a man s ideal is either an idol or a myth In any case, it is easy to recognize that ideals are the most important elements in culture The ideals pursued by a man or a group of men show us clearly the kind of culture they have If the ideals shape the life of a man, we may well say that a man is determined by his culture

I am taking culture as a normative concept in contrast with the positivistic concept of the anthropologist with local and temporal limitations By culture I mean something which man as a rational being ought to achieve in life a good which should be pursued for its own sake It is a clear condemnation of a

man s life that he lacks culture, on the contrary we imply strong praise when we say that a certain person is highly cultured

I would also, as already suggested, emphasize the universal character of culture If culture represents the ideal of human life, it cannot be different for different persons If truth, beauty and goodness are not different for different peoples and coun tries, then the ideal culture which should be an embodiment of these values cannot vary with time and place Different people in their various ways try to approximate to the one supreme ideal of humanity We are worshippers of the same God in our temples and mosques, churches and synagogues

Actually however all men are not equally fitted to pursue the highest ideal of life Man s nature is highly complex According as a particular side of his nature acquires domi nance over his other sides he becomes wedded to the particular mode of life which appears to provide satisfaction to his nature

I cannot critically develop here what I take to be the real human nature I shall be content with stating my views some what dogmatically

Man is patently one with his body, and no man is ever found apart from a physical organism But his whole being cannot be expressed or understood entirely in physical terms In traditional language we can say that he is also mind and spirit or reason We can describe him as a unity of body, mind and spirit If we ignore one of these elements, body or spirit we falsify the real human nature We get either a mere animal, or God but not man

Body stands for the sensible, material part of our being Mind is responsible for consciousness and intelligence and other physical characters which we share in common with the higher animals To spirit or reason we owe whatever concep tions we have of the supreme ideals (or ultimate values) and our sense of loyalty to them At present we have no clear under standing of the relation between these elements of our nature But we know spirit cannot work without intelligence and in telligence or mind cannot operate apart from bodily functions

All these elements though present in every man do not have equal importance We should attach more importance to mind than to body and still more to spirit than to mind In fact one man is better than another only in attaching more importance to the higher parts of his nature

We may symbolically conceive man as a spirit bound to his body His culture or civilization (we might say, his true religion) consists in gradually emancipating himself from the domination of the body or in employing his mind more in realizing spiritual ideals than in satisfying bodily cravings (although no real need of any part of our nature can be wholly ignored) We find that we degrade ourselves and get involved in all sorts of unworthy struggles and conflicts, when we try to acquire more and more material goods instead of trying to realize spiritual values

What are spiritual values? For our purpose we may accept the usual division of consciousness into thinking feeling and willing, each having its characteristic ideal Thinking feeling and willing are functions of the mind when they are concerned with mere facts or ordinary objects When they are directed towards ideals they may truly be called spiritual functions Truth beauty and goodness have traditionally been recognized as the proper ideals of these spiritual functions

These ideals may be differently conceived and formulated but I am convinced that ideals worthy of man cannot be conceived entirely in material terms They are otherworldly in some sense and they lend dignity and worth to our human nature Real culture consists in the increasing realization of these ideals

The most important task of the philosophy of education as I understand it, is to bring to clear consciousness the ideals for which men should live and then to find out the proper means of inculcating them effectively on the minds of young students

Education cannot mean merely the development of our potentialities because there are potentialities for good in us as well as for evil Nor can it mean mere preparation for life because life may be worthy or unworthy Our educators must realize as clearly as possible what kind of potentialities they are to develop in us what kind of life they are to educate us for That is the ideals which constitute the essential elements of culture must first be clearly understood and appreciated

But all are not equally qualified to pursue the highest ideals As we suggested above different people although living in the same country and even belonging to the same family are often at different levels of mental and spiritual development and cannot therefore all attempt to realize the highest ideals

Mere health or physical well being is a good enough ideal for many, some fewer aim at moral and intellectual excellence and still fewer can aspire after higher spirituality In a well ordered society, there should be room for people of different ideals and also provision for the satisfaction of their varying needs

We may not and should not have hide bound castes, but we cannot do away with all distinctions Saints and soldiers scholars and athletes philosophers and merchants cannot all be merged together into a homogeneous mass If we are to avoid chaos and confusion we should have a well understood gradation of classes based on the difference of ideals pursued by them The supremacy however must belong to those who can point to preach and practice the highest spiritual ideals They should guide and control the affairs of men, without being able to derive any material advantages from them Plato s philosopher statesman without any family ties or earthly possessions or the ancient Hindu sage owning no material wealth and yet ruling over kings seems to indicate the kind of people who might bring the present distracted world to a better state

We need not make a fetish of democracy It is after all a form of government or political administration, concerned to regulate our worldly affairs and external public relations It does not touch all sides of our being and cannot supply a motive for the highest activities of our soul Moreover, demo cracy, as it is organized nowadays seems to place the world at the mercy of half educated journalists and unscrupulous financiers This cannot be an ideal state of affairs There should be a rule of reason rather than one of mere number Reason is not equally powerful or acute in all people The number of those who possess reason of the right kind and are willing to be guided by it, and not by prejudice and greed, is limited So when we decide any question by a mere majority, we cannot be sure that we have arrived at a just or rational decision That this is so is apparent from the respect we pay to the opinion of an expert on any question

It may be objected that I have been rather unjust to demo cracy which is not a mere form of government, but a way of life, having aspects which are valuable in themselves For instance, it guarantees the rights of individual men and stands

for freedom and equality, and recognizes the unique value of human personality And these are surely very valuable contributions of democracy to the modern world

I have no desire to decry the valuable services democracy has rendered to humanity My only difficulty is that I fail to see that the values which democracy subserves or specially recognizes, are values of the highest kind or absolute values

I think our duties are more important than our rights and an undue emphasis on the latter may not be quite wholesome We should be earnest rather in discharging our duties than in demanding our rights If everyone did his duty then no occasion might arise for anyone to call attention to his rights

As to equality, I do not clearly see that it is a fact or is desirable in itself In some respect one may be equal to any other As a mutable thing I am equal to the meanest lump of clay The really important question concerns the respect in which one is said to be or should be equal to another And I fail to see that in any important respect there is or can be equality among all men It is only from a superficial point of view that a judge and his hangman may appear to be equal If we look to the range of their understanding or their spiritual depth to the ideals which inspire their whole lives wide differences will easily come to view

Freedom no doubt is a very valuable ideal In the religious as well as the political sphere people have often become, almost literally fanatical about it But have we any positive conception of absolute freedom i e freedom without reference to anything else? Absolutely our conception of freedom appears quite negative as mere absence of restraint or determination Otherwise we understand freedom only in connexion with some function or other e g I am free to talk you are free to go away, etc In the latter case the value of freedom depends on the value of the function in respect of which one is free Freedom to kill or to starve is not easily recognized to be quite so valuable

On this question of freedom it is well to recognize that man as a psychophysical organism or as a member of a social or political whole can never enjoy absolute freedom He is determined by so many factors Physically he is absolutely bound by the laws of nature and his mind too is determined by his physical conditions

True freedom is freedom of spirit We can achieve it only gradually and partially In a certain sense we have freedom even now We are free to will or to think This freedom is highly valuable not so much because of itself, as because of other higher values which require it as their pre condition We cannot achieve goodness or morality unless we are free, we cannot attain truth or knowledge unless we think freely Freedom is instrumental to goodness and truth, which appear to be higher values

I am a humanist in the sense that I believe all values are to be realized in and by human beings and ultimately values do not exist anywhere else But I do not see that any unique value attaches to human personality merely as such if by human personality we understand no more than a centre of conscious ness attached to a body To me human personality is no doubt extremely valuable not however in itself but as the only possible seat for the realization of all spiritual values Since human personality alone has the potentiality to realize all spiritual values it may be supposed to be valuable in itself But we should not forget that it has also the potentiality to be the very picture of the Devil s self on earth an offence to God and humanity Considering therefore his capacities for good and evil I am disposed to regard man as valuable only when, and in so far as, he puts himself at the service of the good

My denial of any ultimate value to human personality need not be considered outrageous for in certain respectable sys tems of thought also, such as Buddhism and Advaitism, our clinging to personality is condemned as evil

Moreover, we know that when a man proves himself to be a scourge to himself as well as to others by some unmitigated vice we feel no qualms of conscience about putting an end to his life People often sacrifice their lives for their country, for freedom and truth If human personality were such an inval uable thing, it would not perhaps be sacrificed in this way Every day, perhaps every minute thousands are born and thousands also pass away Such profuse production of unique values and wanton destruction of them would be staggering indeed It would not be reasonable to argue that human personality, as human, extends beyond birth and death

I may be altogether wrong in my view of democracy and of the values it subserves My main point is whether it is

wholly rational in its ways If as a way of life, democracy is inspired, guided and controlled by reason, I can have nothing whatever to say against it

Reason should be broadly conceived not merely as a capacity for argument only but as the principle of intellectual enlightenment as well as of moral inspiration, as both theoretical and practical The most important thing is to make the rule of reason prevail in our individual lives as well as in the life of the community If we can make reason dominate our life we shall no longer be guided by unproved and unfounded beliefs whether in religion or in politics and shall never sacrifice higher values for the sake of lower ones Dogmatic religions with definite and conflicting creeds which led to wars in the past will be steadily at a discount

It should not be supposed that I wish to eliminate all religion from a life of higher culture Religion in the sense of passionate apprehension of spiritual ideals and a sincere attempt to realize them in life, is itself the highest form of culture of which I can conceive Religion as the best way of life possible for a man is bound to remain at least as an ideal as long as there is a spark of reason in man But organized religion involving particular beliefs that can hardly be justified at the bar of reason can no longer be accepted by men who make reason the rule of their life Religion in the ordinary acceptance of the term always involves a set of dogmas which are hardly credible and enjoins certain practices which seem to have no moral significance If we had just one set of beliefs and practices prevalent throughout the world, there would perhaps be no serious danger in them But in point of fact there are different sets of beliefs and practices sanctioned by different religions and when a person accepts one such set as forming his religion he is bound to regard it as the best and superior to all others This leads to hatred and conflicts especially when proselytizing zeal is added to religious faith Religion has thus often worked as a divisive force in history against culture and humanity I therefore think that religion in this sense will be favoured less and less by men of real culture

I do not however forget the services rendered by religion to culture in the past Music and poetry painting and architecture, flourished on the basis of religion Philosophy was the pursuit of religious men and medieval schoolmen with their

religious zeal, were the spiritual forefathers of our modern scientists In India too, religion philosophy and science were for long a combined interest Morality everywhere drew its inspiration from religion, and many a barbarian was humanized by religion alone But with the maturity of human reason all these cultural forces science and philosophy, art and morality, have broken free from religion and are running their own independent courses and fulfilling, in their different ways the cultural functions which were once performed by religion The independent cultural value of religion now thus seems to have dwindled to a minimum If one follows art and morality, science and philosophy in a religious spirit i e with genuine devotion and sincerity, one need have no separate religion at all

A word on science may not be out of place here Science as the disinterested pursuit of truth for its own sake is no doubt a thing of the highest value and should never be depreciated But the prestige of science in the contemporary world seems to be largely due to the services it renders to militarists and industrialists This makes it suspect in the eyes of all right thinking men Further when we enquire closely, we find that the ideal of knowledge, which science pursues is not pure or mere knowledge but knowledge which is power There is no denying the fact that power has a corrupting influence When you pursue knowledge not for its own sake, but for the sake of the power it brings you to dominate nature (and men), you have already started on a wrong path with a perverted mentality It is therefore no surprise to find the great harm science has done and is doing to the spirit of man, as an ally of unholy powers as an engine of destruction, as an instrument of exploitation and profit

One cannot of course be blind to the wonders science has performed or to the obvious material advantages man has derived from it But a man of reflection cannot also fail to note how little science has contributed to the higher and spiritual needs of man All its triumphs are on the material plane Spiritually man has not been made better than his forefathers Peace and tranquillity charity and justice as well as other virtues of mind and spirit, have not been quite as abundant in the scientific age as one would wish them to be

There is yet another kind of unspirituality connected with

the spirit of science It assumes that everything is knowable and is in principle sensible that our intellect is sufficient to cope with all *aspects of reality I conceive it to be a moral duty* of all intelligent persons to carry forward the work of intellectual analysis and understanding as far as it will go, and we cannot recognize any arbitrary limit beforehand But this is different from supposing, as science seems to do, that there cannot exist any mysteries in reality which we may be unable to solve This is likely to breed intellectual arrogance and lack of genuine humility

However it is too late in the day to wish to stop the progress of science in the modern world It has entwined itself too intimately with our present way of life What we can do is to put it in its proper place It is certainly a very useful tool in our hands by means of which we can satisfy many of our physical or bodily needs, and it should by all means be preserved as long as we cannot deny our bodily self But as body takes a subordinate place to mind and spirit, so the place of science is, and should be lower than that of other disciplines which are concerned with our mental and spiritual needs such as art and morality, religion (in the best sense) and philosophy

I *should however* admit that science in the sense of disinterested pursuit of knowledge for its own sake must always remain in the highest rank along with religion (in the best sense) and philosophy with art and morality as an essential form of culture In all these spheres our ultimate loyalty is to *the ideal of reason which speaks directly to the spirit of man* in the language of truth beauty and goodness without the aid of any extraneous revelation which we may call by any of these names or by some other such as "sweetness and light or even love or God but whatever the name it always appeals spontaneously to our *better sense (or reason) as alone deserving* and demanding realization absolutely on its own account

Culture is a way of life and thought inspired by rational ideals Education is the initiation of man into the life of culture Its aim, as I like to conceive it is to awaken the mind of man to a consciousness of worthy *(rational or spiritual) ideals and to a* lively interest in their progressive realization It seeks in Plato s language, to turn the eye of the mind towards light the light which dissipates the darkness of ignorance and prejudice that breeding ground of all the diverse ills of our life

Theory and Practice of Education in the United States

by

CLARENCE H FAUST

EDUCATION in the United States is not the expression of a single coherent set of beliefs about the nature of man and society Practices differ widely at all levels of education, in both public and private institutions and these differences of practice reflect a variety of opinions and beliefs among educators and interested laymen concerning the nature and purposes of education Conflicting theories concerning the responsibility of schools for providing vocational training social experience, and religious instruction lead to wide differences in the scope of school activities Conflicting theories concerning the roles of reason and emotion and the relative importance of reading and first hand experience in education lead to wide differences in methods of instruction

Conflicting principles frequently in greatly simplified and incomplete versions of basic philosophic differences lie behind the variety of vigorously opposed educational movements in the country One movement would make the schools student centred rather than subject centred by devising educational practices to fit the individual differences of students, rather than arranging curricula in accordance with historic departments of knowledge Another would reform school curricula by analysing the particular life needs of students and reshaping or replacing conventional courses in accordance with specific activities in which students will engage after their formal schooling Another movement would provide students with a common body of knowledge and competence in reasoned discussion in order to establish the basis of intellectual community for dealing with the basic common problems of our time

As a result of these differences of opinion and belief concerning the scope, the nature, and the purposes of education

students of the same age receive very different kinds of educa tion in the United States They may be given very considerable religious instruction, or none at all They may be required to pursue a very precisely prescribed course of study, or they may be permitted to determine what they shall study and how they shall study it Their education may be chiefly vocational, or include no vocational training at all Much time may be given to books and to reading, writing, and arithmetic or such study may be condemned as verbal and academic and replaced by organized social and physical experience

More fundamental than the conflict of theories which gives rise to this variety of educational practices—and more clearly indicative of the fundamental tensions in American life and thought which are observable in ethics, politics and aesthetics as well as in education—is the controversy over absolutes' the debate concerning the validity and usefulness of timeless and universal principles of thought and action Two concerns have frequently been in real or apparent opposition in the development of thought and activity in the United States One has been the concern for finding effective ways of securing immediate and specific results amid rapidly changing circum stances as the people of the nation have swept across a conti nent which presented to each new surging group of pioneers both new possibilities and new dangers The other has been the search for timeless general principles and criteria as guides for understanding and coping with the bewildering complexities of changing social and physical experience

Religion with its concern for relationship to an eternal and unchanging being and for absolute criteria of excellence, was central in the thought and practice of many of the founders of the colonies on both seaboards of the country and it continues even in secular forms and in fragments of theological beliefs surviving in secular thought, to exert an important influence The concern on the other hand, for survival and success under circumstances of life in a new land exhibited in the first of these traditions has deeply marked the ideas and institutions of the nation

As between these two traditions, the people of the United States have undoubtedly been increasingly preoccupied with the latter, that is, with processes, with the ways in which sequences of events may be understood and the knowledge of

them applied under particular circumstances to the direction of particular means to immediate ends And American philosophy has been increasingly interested in the processes by which things happen or may be brought about, increasingly disposed to formulate criteria of excellence in terms of concrete and temporal effects, and increasingly disposed to refer questions of the truth of opinions and theories to the consequences of holding them or at least to view propositions so attested as more substantial and valuable than those otherwise established

Preoccupation with process exhibits itself, moreover, in the kinds of study or research in the humanities, in the social sciences and to a lesser extent in the physical sciences which have come to be most highly regarded in American colleges and universities What seems most important to many scholars working in literature and the arts are the circumstances in the experience or opinions of an author, or in the life and particular ideas of his time, which may be construed as causal explanations of the traits of his work The details of the life of a poet or the special practices and conventions of the stage at a particular period, or the development of popular interest in certain forms of the short story in America—subjects such as these, rather than the criteria of excellence in literature or their application to individual literary works, are the commonest problems of literary scholarship in the United States This interest in untangling and clarifying particular causes in relation to particular effects in literary history is an aspect of preoccupation with process A similar preoccupation is evident in scholarship in the social sciences when anthropologists describe in detail the habits of certain societies when sociologists explore empirically the class structure of society, the formation of public opinion the operation of mass media of communication, or the causes of failure in marriage, when political scientists analyse administrative structures and procedures and when economists concern themselves with the operations of price, production labour management, and money policies In education itself when made the subject of research, the concern is predominantly with problems of motivation the steps of the learning process, teaching devices and administrative procedures

This preoccupation with process with the particular ways

in which things come about or may be brought about directs attention both in research and in teaching to the particular and the temporal rather than to the general and timeless What is very generally sought in research and what is presented in the classroom is the clarification of causal relationships among specific sequences of events rather than general principles of timeless significance For a large and influential group the discovery of such sequences constitutes not only real knowledge but the only real knowledge Pursuit of timeless principles is regarded as both futile and impractical No such principles exist it is held and if they did, they would be too remote from the immediate and concrete problems which require solution to be of any practical value To look for them is to divert attention from the urgent problems at hand

In this view the immediate problem of satisfactory relations with nations and peoples of other cultures is not to be solved by reference to some set of universal principles concerning mankind, to the potentialities of human beings as members of the human race, or to general principles of justice in human affairs The feeling concerning the futility and even the positive danger of attempting to establish universal principles as guides for action is so strong and so generally accepted that to accuse a thinker of implying absolutes is sufficient in many quarters to cast serious doubts upon his ideas The situation is illustrated by the handling in America of the commonest approach to the problems of intercultural or international relations through what are called area studies The subjects of such studies are the particular history of a region its particular laws and customs its particular social and political structure its particular language and its particular philosophy Equipped with knowledge of these matters the expert in an area is assumed to have at his command what would be needed to determine national policy with respect to the area to function as an administrator of programmes of activity in the area or to provide any assistance which the people of the country may seek or need

The concern with process as an object of knowledge affects the methods by which knowledge is thought to be acquired and communicated The method must be empirical in the sense of depending upon the acquisition of masses of specific data It may be experimental by way of the formulation of an

hypothesis and the setting up of conditions under which observable fact may be expected to validate or disprove the hypothesis The key to validity in this method of reaching truth is predictability Truth has been discovered when it is possible to set going a sequence of particulars with confidence concerning the phenomena it will exhibit in its later stages, or, where the sequence cannot be manipulated, with confidence that once its initial stages have been observed, succeeding ones may be correctly anticipated The experimental method may be supplemented by the historical, and the problem of history then becomes that of identifying separate cause and effect relationships in the developments of society political institutions, and the arts

It follows as a consequence of commitment to these methods of securing insight that the best to be hoped for in the study of human behaviour and institutions is a high degree of probability Absolute knowledge is no more possible than the existence of absolute principles Demonstration, as opposed to probability, is possible only in precise subjects such as mathematics Abstract reasoning that is reasoning which does not rest upon observed fact may be an interesting intellectual pastime, but like absolute principles has little practical value except in the sphere of mathematics where constructions of ideas may prove their value in providing the terms for precise predictability of physical events That the knowledge sought in research and communicated to students does not rise above probability of success is, of course not a matter of serious concern to those preoccupied with process The end of knowledge, in this view, is guidance for action in certain complex circumstances, each cluster of which is to a degree unique The pursuit of knowledge always begins with a specific problem The solution of the problem is the end in view Since the problem is particular and its solution involves the discovery of the way in which relevant special circumstances can be met or handled, probability is as much as can be expected and is as nearly adequate to the situation as knowledge can be To seek timeless principles for application to the bewildering succession of unique problems which the individual and society face is to court the danger of embarking upon actions inadequate to the peculiarities of the temporal situation

The seeker after knowledge must, then, be an experimenter

And he must be aware that he is, himself, embedded in the processes of history The problems which it seems important to him to solve, as well as the solutions which suggest themselves to him, are consequences of his individual situation in time, place and culture The factors which have determined his outlook his interests his equipment of ideas and his methods of dealing with his problem make all that he does relative to his personal place in history *Any attempt to surmount* these limitations would itself, be only a consequence of his situation His reason is limited if not determined in its content and operation, by these circumstances Education must, consequently, make no pretence of developing a competence *for the determination of absolute truth It must be* concerned with the student s social adjustment and the removal of psychological tensions It must begin with the interests he exhibits discipline him to avoid prejudice and dogmatism in favour of careful survey of empirical evidence and teach him to regard his own and other people s conclusions as at best probable and as in all cases largely determined by his individual environment and temperament It should be practical in its attention to the details of vocational training and more inclusively, to the whole range of his particular life needs

All this, however is but one strain in American thought and the theory and practice of education in America can by no means be wholly explained by it The preoccupation with process has throughout the history of the American people been accompanied by a quite different concern a concern not with sequences of particulars but with the relations of the temporal and particular to the eternal and universal Theologians such as Jonathan Edwards have sought to determine in what respects and how far human beings as temporal existences participate in absolute being in what respects and how far individual human lives coming into existence in time and place share in the being of that which must always have existed, the totality which itself did not come into being but *simply is* The *temporal* beings which particularize its existence in time and place must according to this line of thought find their most important knowledge in insights concerning their relationship to it For philosophers such as Emerson such knowledge is more important and more real than the

shimmering sensation of particulars or empirical determinations concerning the sequences of particulars Poets of the school of Walt Whitman tend, on the other hand, to find the universal and the ultimate in nature rather than in some being of which nature is the expression or projection or emanation

It is assumed by these writers, and is fundamental in the tradition they represent that knowledge of man s participation in universal being is possible It could not, of course, be acquired by even the most precise insights into the sequences of particulars which constitute temporal experience But even as mankind has a capacity for apprehending the particulars of sense experience, so it has a capacity for laying hold upon absolute being and absolute truth The means of achieving such knowledge have been variously conceived of and named —the operation of discursive reason, the activities of poetic imagination, or the insights of common sense The methods of securing knowledge of eternal being and a grasp of timeless principles may range from rigorous practice of abstract thinking to the cultivation of mystical experience, or the clarification of the ideas of common sense which are considered available even to the meanest human capacities

It is in this tradition that much of the theology and much of the early political theory of the United States was developed When the people of the 13 original colonies declared their independence of Great Britain they began by announcing that certain general truths were self evident All men they declared are created free and equal and have certain inalienable natural rights among which are life, liberty, and the pursuit of happiness It would have seemed to the founding fathers of the country insufficient unconvincing and wholly inadequate to say that given the peculiar circumstances of life in America in 1776 and given the particular inheritance of desires interests and ideas separation from the mother country was probably justified

Both of these two strains of thought in America, the preoccupation with process and the concern for participation in absolute being have applied themselves to religious and to secular problems While one wing of puritan thought best represented perhaps by Jonathan Edwards centred upon the possibility of spiritual union with God conceived as "Absolute

Mind , another, best represented by Cotton Mather, was preoccupied with the discovery of historical and contemporary activities by means of which human beings might become instruments or agents in the plan of operations formulated by the Deity The second school held that the ultimate nature of the universe was beyond human comprehension, that the divine plan for its operations was beyond the power of human thought, and that it was presumptuous for finite human beings to inquire into ultimate ends Religion for this school was not absorption in eternal being but adjustment to an eternal plan of operation Virtue was not union with or participation in the divine and absolute but willing activity as an agent or in strument of specific divine purposes

As religion has been pursued along these two lines so at the other extreme has the interest in nature Man is understood to have reached what degree of perfection is possible for him by absorption in nature by developing or yielding to what he shares with the natural world by participating as fully as possible in nature or as Emerson put it permitting the cur rents of universal being to flow through him The predominant thought, however, of the past few generations in the United States concerning man s relation to nature has centred upon the possibilities of human adjustment to the processes of nature or special devices for human mastery of it The problem of human life has increasingly been envisaged as a matter of meeting particular and rare situations by particular and immediate processes of adjustment to them General questions concerning the consideration of ultimate ends of nature and attempts to operate on the basis of absolute principles have from this point of view seemed futile and even positively dan gerous

Contemporary American thought and practice would be misrepresented however if it were pictured as a conflict of two schools of thought consistently and sharply opposed to each other The universal principles which one school seeks have their value not merely in participation in absolute being and intelligence but also as guides for immediate and specific activities Religious men concerned about man s relation to ultimate being have in the light of the principles they regard as universal engaged strenuously in the construction of par ticular religious institutions and the formation of detailed

codes of conduct The purely contemplative soul is rare in the United States

On the other hand the theory and practice of those pre occupied with processes have not been wholly divorced from general and even universal ends Ends and values have often been implicitly assumed and permitted to remain inexplicit and unexamined The earnest pursuit of particular knowledge and useful practice in biology and medicine for example has assumed that physical life and physical health are values for all men in all times and places These assumptions can be chal lenged Every suicide does challenge them But they are not explicitly examined in our schools of medicine In the case of education the assertion that it is futile to consider absolute values and ends is commonly accompanied by a declaration of the importance of individual maturity and growth and of social cohesion and strength For these ideals of individual growth and social strength owe their significance to the tradi tions of thought necessary to the discovery of universal and absolute values and ends So too does the very common term adjustment which means more than the mere absence of friction, and involves in an unexamined general way concepts of desirable relationships inherited or borrowed from the traditions of thought concerned with explicit formulation of universal ends and values

One consequence of this situation is a certain embarrassment in many circles in the United States concerning talk about those ultimate values which our activities assume In the tradition of preoccupation with particular processes talk about absolute principles is regarded as futile and pretentious Yet leaders of religious, political or economic thought are in this respect granted a certain tolerance when they engage in public pronouncements and are indeed expected to enunciate general ends and values The man of affairs who in his office or among his associates would be uncomfortable in the discussion of general principles of justice, for example, and wholly inexpert in pursuing or presenting a sequence of thought regarding them is to some extent released from this embarrassment when he makes a formal public speech, and feels moreover responsible for declarations of general principles

Concern for the spiritual as against the material is likewise not the exclusive property of one school of thought in the

United States It has often been pointed out that despite the preoccupation with spiritual matters of important leaders and groups among the founders of the country, the practical activities of these men in the conquest of the continent and in the erection of a highly complex material civilization were tremendous Conversely the rewards sought in the most materialistic of American activities the acquisition of fortunes for example seem often to have been satisfactions which were basically non material

It is not surprising that educational practice in the United States should present an appearance of confusion and conflict The institutions established to induct the young into the life and culture of the country reflect the tensions between preoccupation with process and concern for participation in the universal Despite these conflicts the interest on the one hand of all parties in the immediate practical operations of educa tion and the adherence, on the other hand, even of those who repudiate absolute principles to certain unexpressed and un examined general values prevent the educational system from falling to pieces under the strains in American thought which it reflects It should be added that the country s tradition of freedom of thought and discussion is of inestimable value in providing the possibilities for the reasonable resolution of educational conflicts

The greatest need of American education is the clarification of the relationships of the various philosophies it expresses What is required is the investigation on the one hand of unexamined principles and values which play their role in the determination of educational practices and the fuller investi gation on the other hand of universal principles values and criteria with a view to more detailed practical application of them These too, may be among the basic needs for the development of fuller mutual understanding between East and West

The Concept of Gradual Progress in Indian and Western Philosophy

by

HELMUTH VON GLASENAPP

WITH the heavens above his head and the earth beneath his feet, man stands in the midst of the universe Himself drawn to the depths by the force of his material body but at the same time raised to sublime heights by the lofty aspirations of his mind since time immemorial he has tried to solve the three riddles about himself which Immanuel Kant has formulated in the questions What can I know? , What shall I do? and What may I hope? The answers that have been given to these questions since the time when primitive man tried to make out his position in the world to determine what is good and bad and to solve the mysteries of death, have been very different and always provisional For the particularities of space and time of blood and tradition as well as the peculiar inclinations and predilections of individual thinkers, have produced a countless variety of religious teachings and metaphysical systems which have all claimed to have removed the veil hiding the face of truth

And yet if we consider the history of man s endeavours to pin down the truth, we come to the conclusion that however much thinkers differ in their interpretation of the nature of the universe and that which is beyond it nevertheless they all agree to some extent in the practical conclusion in recommending a life which would in fact comply with the requirements of society and of man s own conscience This insight has been expressed in the *Subhashitárnava* in a beautiful verse which runs as follows

> Concerning sacred places concerning God and concerning religious duties there is discussion among the wise but there is full harmony with all systems in the commandment do good to everybody and honour your parents

It is clear that a high moral standard is not attained immediately, *only gradually* It requires education to develop a child subject to various and conflicting impulses into an adult obeying the laws of ethics It is one of the most productive thoughts in the history of religion and philosophy that man as he comes from the womb of nature has a long way to go until he reaches perfection, and that the highest level can be reached only step by step and by passing through many grades This concept of the possibility of a gradual progress is not only a sound principle of secular and moral education it plays an equally prominent role in man s endeavours to transcend the bounds of his earthly limitations and to advance to the realm of the divine But how can man hope to attain so high a goal without knowing his true position in the world and among his fellow beings? The practical side of life has always to be supplemented by theoretical knowledge We have therefore also to deal with the concept of graduation in its biological and historical aspects Finally having considered the multiple views of scholars of many ages and countries we have to show one thing more We have to ask ourselves whether *all* the conflicting statements on and interpretations of, the world must be understood as forming successive steps leading to the metaphysical truth propounded by individual thinkers or by a special school of thought

Being neither a philosopher nor a theologian I do not intend to proclaim new truth or convert anyone to a particular system As a historian my task is more modest All I desire is to show how the idea of graduation and of gradual progress is realized in all the essential domains of philosophy in so far as they are concerned with presenting a great ideal to man and raising him to a higher level of ethics and understanding

In *considering* the world of today we see that four great civilizations dominate the greater part of the globe the civilization of the Far East Indian civilization Moslem civilization and Western civilization Each has produced a philosophy of high standing In Europe the philosophy of the Arabs was known as early as the Middle Ages when Ibn Sina (Avicenna) and Ibn Rushd (Averroes) were studied by Albertus Magnus and Thomas Aquinas Chinese philosophy reached Europe in the seventeenth century, when Catholic Fathers translated the classical texts and Leibnitz and Wolff

sung its praises The study of Indian philosophy was the last to be begun in modern Europe, though the ancient Greeks had some knowledge of it Its pioneers were Anquetil Duperron, Charles Wilkins and H Th Colebrooks, its heralds Schelling and Schopenhauer

It is to be regretted that after these promising beginnings Western philosophers of our times should give inadequate consideration to the metaphysics of the East This must be deplored for if it is the task of philosophy to occupy itself with the problem of the entire world and the whole of humanity, and to depict the achievements of thought universally, it cannot neglect what has been done outside of Europe and America Today when Asia and the West are connected by aeroplanes which make short work of space today, when we can contact the scholars of the whole earth there is urgent need for all philosophers to know about each other and to acquire at least some knowledge of the results of thought reached in the Orient I shall therefore in this article compare the teachings of the Occident with those of the East In referring chiefly to Indian philosophy, I do so for personal reasons For, although I have visited Turkey and Egypt China and Japan and have read Islamic and Far Eastern philosophers in translations I feel more familiar with the philosophy of Hinduism, Jainism and Buddhism because I have devoted my life to their study It seems to me also only right to deal in the first place with the thoughts of this hospitable country to which we are invited, whose wise men have, with indefatigable zeal since the times of the Upanishads of Mahavira and of the Buddha, devoted all their lives to philosophy and religion

The great ocean deepens gradually but not abruptly and steeply So there is also in good teaching and discipline a gradual instruction a gradual practical application and a gradual progress These words of the Buddha give in a nutshell the principles of education applied all over the world, in the schools of ancient Greece where the boys received their physical and literary training after leaving their mother s knees at the age of seven, in the palace schools of Charlemagne as well as in the modern Western educational institutions, from the kindergarten to the grammar school and the university

These principles were applied also in ancient India where

primary education began in the *pathshalas* or in the monasteries in which the pupils learned the three R s and proceeded then to higher studies The famous Chinese travellers Fa Hien and Hiuen Tsiang and I tsing have left us remarkable pictures of the efficiency of the universities of Nalanda and other places of Buddhist learning I tsing tells us that the course of instruction for boys began with the study of grammar to which three years were devoted followed by the study of commentaries and works of a more advanced character He compares the stages of the student with the several degrees of the Confucian scholar

The aim of Eastern and Western education has always been the same the purposeful transmission of the learning and culture of one generation to qualified successors The methods also have been identical in India and Europe A celebrated verse attributed to Chanakya (Bohtlingk *Indische Spruche* 2 ed Nr 5848) says that for five years one may fondle a son for 10 years one may spank him, but when he has reached the sixteenth year, one may consider him a friend This harmonizes with the theories of modern Western educationists, who say that during the first six years the child should be induced to good habits by coaxing, in the second period his character should be moulded by obedience enforced by punishment if necessary, but that in the third period commendation is the principal means of training

The fundamental goal of education is not only to impart knowledge but to develop a moral character to lead the individual to the perfection of his abilities and powers in a word, to give him a complete possibility of self realization in the widest and truest sense of the term For this reason education should not stop at a certain age, when the course of studies is finished, but should continue throughout the whole of life Every nation has worked out for this purpose its own ways and methods The most original and noteworthy of these is to my mind the Indian system of *áshramas* that prevailed during the time of the Upanishads

According to this, the young Aryan i e member of the higher castes was at the age of 8 or 10 years sent to the house of a Brahman to live there and be taught the *Veda* There he remained for 12 years or more, his time being divided between the studying of the holy texts and the fulfilment of domestic and religious duties When he had finished his

studies he left the first *ashrama*, that of a *brahmacharin*, and entered into the *ashrama* of a *grihastha*, i e a householder He married and founded a family for it was considered a religious duty to beget a son that the thread of his race be not broken as the Taittiriya Upanishad I 11 says But when he developed wrinkles and grey hair and had seen the child of his child, he must give up all worldly pursuits and retire to the woods As a *vanaprastha* he lived, with or without his wife, free from al most all duties and sacrificial obligations, a religious life given to meditation The last stage of the career of the pious Aryan was that of a *sannyasin*, a man who had cast off everything from himself As an ascetic he wandered from village to village until death removed the last barrier that prevented his absorption into the Brahma, the universal spirit

Later on this system of *ashramas* fell into disuse today, as far as I know it is little more than a survival But the attempt it made to transform human life into a preparatory school for eternity (Deussen) merits the highest admiration For it gave the *grihastha* all the possibilities of enjoying life and seeing its sorrows until he felt himself ripe to sever gradually the bonds of attachment to it The system of the *ashramas* stands perhaps unique in the world and even if it has become obsolete now, it shows the lofty spiritual ideal of the ancient Indians who made the whole of life subservient to the conception that it is not the destiny of man to be submerged by worldly cares, but to raise himself above them to a higher sphere

In many religious systems from the secret societies of the Primitives to the modern Freemasons, there has been a number of grades which the adherent must pass through from the state of the worldly to that of the fully initiated man Members of the several grades are expected to possess a progres ively more elaborate knowledge of the religious truth propounded by the individual system these grades often being distinguished by their dress or by special symbols

As these matters are closely connected with rituals, we cannot go into details here But we may deal with another *subject that is of great importance in every system of mystical* philosophy, namely the different steps which are to be dis tinguished on the way to the transcendent truth The Indian theists e g the *Bhagavatas*, teach that there are five dominant emotions directed to the Supreme, and these are arranged in

ascending scale (1) renunciation of the world, (2) obedience, *dasya*, servitude, (3) *sakhya*, friendship (4) *vatsalya*, the tender fondness of a child and (5) *rati*, or passionate love The idea that man when he tries to penetrate more and more into the essence of God passes from the position of a servant to that of a friend, from that of a friend to that of a child and from that of a child to that of a lover shows a parallel with Angelus Silesius and other Christian mystics

In Indian works which expound a monistic doctrine of the identity of the individual spirit and the absolute theories on the steps leading to the supreme goal have also been developed I may quote here only the *Yogavasishta Ramayana* according to which there are seven stages of *bhumikas* that mark the path to salvation They are (according to III 118) (1) *Subhechchha*, the striving for the good, (2) *vicharana* philosophical reflection (3) *tanu manasa* small activity of worldly thought because of detachment from sense objects (4) *sattvapatti*, attainment of the true self existent entity, (5) *asamsakti* severing of all bonds to the world as a consequence of the *chamatkara*, or surprise felt at the union with the infinite Spirit (6) *padarthabhavana*, the state when the perception of the plurality of objects has ceased (7) *turyaga* the state of objectless contemplation which is the preliminary step towards the definite end of individuality reached at death only

This ladder of mystic states and perfections has its counter part in neo-Platonism Moslem Sufism and Christian mysticism Strenuous and prolonged self discipline is in every case the precursor of active contemplation This consists of a long process of internal quietude of abstraction from sense and of absorption in the transcendent till the human soul is attuned to the divine By this act of contemplation the whole personality is raised to a higher level in so far as the abysmal depths of its existence are reached the foundation or bottom of the soul which finds its repose in the infinity of God

In Buddhism we meet with similar methods By a life in retirement and indifference to all worldly desires the disciple has to prepare the way for the contemplation of the truth all is impermanent, all is without self all is therefore full of sorrow It is the salient feature of Buddhist philosophy that it acknowledges neither an immortal soul as the centre of the so-called empirical personality nor a personal God who rules

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the world nor an impersonal absolute out of which the universe has developed For this reason, the Buddhist method of reaching salvation cannot consist in the elimination of all elements which do not belong to the soul as the very nucleus of the individual nor in the pantheistic merging of the individ ual spirit in a universal spirit The way to truth has as its presupposition the knowledge that there is no substantial entity in this world of universal flux Man is a complex of *dharmas*, of changing constitutive elements which arise accord ing to moral laws in functional dependence on each other The aim of the thinker consists in gradually realizing the truth, that there is no self The Buddhist philosophers in contra distinction to the Vedantins and others believe that the expunging of the idea of self is the necessary forerunner to the attainment of *nirvana*

It is interesting to note how this doctrine that there is no ego has produced quite different effects in the history of Buddhist thought In ancient Buddhism, it found its ideal representative in the *arhat*, in the saint who lives as a hermit or in a monastery entirely given to spiritual exercises In Mahayana Buddhism, the negation of the ego is a call to greater moral activity, because the aspirant towards a higher life understanding that there is no difference between himself and his neighbour must develop the wish to do good permanently to others According to the elaborate theories of the stages in the career of a *Bodhisattva* an aspirant for future Buddhahood develops step by step all the eight cardinal virtues until he becomes a saint This saint, having liberated himself from all egotism, in his turn frees other creatures from egotism and makes them mature for the cultivation of moral perfections which will lead them also to salvation

The Buddhist doctrine of the non existence of a self has no counterpart in Western philosophy though we find also in Hume, Lichtenberg and Mach the conception that the ego is as transitory as the body The practical conclusion from it would seem to be that one must not attach any importance to the ego, but by getting rid of this erroneous idea devote all one s endeavours to the welfare of other beings

Orthodox Christianity teaches that man can perfect himself only in his existence on earth When his life has come to its end he earns the fruits of his moral behaviour either immediately

after death in heaven or hell by the special judgment of God or at the end of time when the dead are resurrected In India, the doctrine of transmigration is the basis of the systems of Hinduism, Jainism and Buddhism According to this belief, every individual after death enters upon a new existence In this life, he earns the fruits of merits acquired in the past and has to endure the consequences of sins previously committed

We have not to embark here upon an explanation of the philosophical theories which try to define which is the factor that wanders from one existence to another or how the rebirth is effected Hindus and Jains on the one side, and Buddhists on the other, disagree on this The former believe in immortal souls and their reincarnation The Buddhists deny the existence of immortal souls capable of survival but acknowledge a series of momentary entities or *dharmas* which pass from the dead to the being to be born So the man who is reborn is not the dead one on the other hand he is also not different from him because he originates from him But there is conformity in all Indian religions in so far as they emphatically believe that as a man sows so he reaps There is a moral and natural law, inherent in the universe the outcome of which is that every act voluntarily done by man has its consequences in a new life which succeeds the present one

According to Indian philosophers, this doctrine of *Karma* gives a plausible explanation of the diversity of human conditions and human fate This teaching is eminently moral because it explains the whole world development as the necessary result of the combined acts of all beings taken together and it includes the three possibilities which are necessary for the recognition of a moral order of the world the possibility that man is responsible for his doings because he has a free will, the possibility that there is a just retribution for everything done by him and the possibility that his insight and moral behaviour will ripen more and more so that he may become perfect after thousands of existences The doctrine of *Karma* rightly understood thus considers every existence as a stage on the way to perfection

It is well known that this doctrine of transmigration has also found followers among the adherents of other religions such as the ancient Celts and Teutons, some Jewish and Mohammedan mystics and some Christian heresies Among ancient

European philosophers, Pythagoras, Empedocles, Plato and Plotinus were its exponents In modern times, the doctrine of a gradual progress by the individual through many lives in succession was advocated by two famous German writers at the end of the eighteenth century Lessing and Kant Lessing says in his work, the *Education of the Human Race* (1780) that as a man cannot in one and the same lifetime pass through all the stages towards perfection he has to experience many existences Similar is the opinion of Kant in his *Critique of Practical Reason* He argues that the categorical imperative demands of us perfect morality and perfect holiness This cannot be realized in one life, and therefore presupposes that our personality lasts for an infinite time and that we have to reach the goal in a successive approach of infinite progression It was Paul Deussen who remarked that this agrees with the verse of the *Gita* (VI 45)

> *Striving zealously with sins cleansed the disciplined man perfected through many rebirths finally goes to the highest goal* [1]

So far I have only dealt with the different conceptions of the gradual progress of the individual now I shall speak about the theories that assume a collective gradual progress The most important of these is Darwinism the doctrine of evolution associated with Charles Darwin who published his *Origin of Species* in 1859 According to this work evolution in nature is the result of selection in the struggle for existence Basing themselves on this theory scientists have tried to establish a pedigree of the human race and to show that there is an ascending scale beginning with the lowest types of living beings and ending with man This doctrine contradicts both former scientific opinions upholding the invariability of species, and the beliefs of all the great religions It had its precursors in some Greek Chinese and Mohammedan mystics who anticipated the idea to some extent but it is a modern Western achievement It caused a change in all departments of Western knowledge almost without parallel in the history of thought Its philosophical importance is that it eliminated the essential difference hitherto supposed to exist between man and animal and taught instead a gradual

1 Edgerton's translation.

progress in the nature of species an ascent from simpler forms under the stress of competition for the necessities of life

The basic conception of Darwinism that all life is one great entity, is of course not new to Indian philosophy For already in the Upanishads the Hindus were of the opinion that plants and animals have a soul like men and the Jains had a presentiment of the modern theories of the existence of infinitely small living beings like infusoria and bacteria It is therefore not astonishing that in the third century B C the emperor Ashoka built hospitals for animals In the West some Christian saints like Jerome and Francis are recorded to have cherished a brotherly love for the brute creation but societies for preventing cruelty to animals have existed in Europe only since the beginning of the last century

Theologians and philosophers in the countries west of the Hindukush have always tried to conceive of human history as a process beginning with the creation of the world and ending with the destruction of the present universe the resurrection of the dead and the coming of a definite state of everlasting and immortal bliss Zarathustra and the later Jewish prophets were protagonists of this theory of world history and Christianity has made this doctrine one of its chief teachings Saint Augustine in his De civitate Dei has laid the foundations of a philosophy of history that considers the 6 000 years forming the term of life of mankind as being the progressive realization of the Kingdom of God

In the nineteenth century this idea was transformed into a philosophical theory of evolution According to Hegel the whole of history is a development teleologically conceived for the end governs the process As the germ carries within itself the whole nature of the tree the flavour and the form of the fruits so the first vestiges of mind virtually contain the whole of history History is thus the necessary evolution of the immanent idea the process being fixed in all its stages Through human interests and actions the final purpose of history is carried out but the purpose itself is beyond human interests and actions

It is the heritage of the Christian philosophy of history that Hegel does not assume that evolution goes on for ever but that he thinks that a highest and absolute form may be reached So he takes Christianity to be the absolute form of religion as his own philosophy is the absolute philosophy After having

passed from one phase to the other, the human mind at last reaches a sort of plateau where it will continue for ever on an elevated plane The followers of Hegel split later into two groups The idealists conceived history as an evolution of consciousness in an optimistic way, but with Eduard von Hartmann, the philosophy of history acquires a pessimistic trend Existence is governed by a great unconscious which, as a universal providence, guides all issues to a predetermined end The aim of the unconscious God is his redemption a universal *Nirvana* or evanescence of the total volition of the world into nothingness Other philosophers starting with Hegel worked out a materialistic conception of history For the Hegelian *dialectic of the absolute idea, Karl Marx substituted a dialectic* of economic conditions and development The ideal elements in man s nature and life are reflexes only of the interplay of material conditions and economic facts This materialistic conception of history is obviously hostile to all theories of a spiritual origin or destiny of man Nevertheless the faith that in the future a new, just order will rule the world gives to the Marxian theories some similarity to the religious expectation of a renewal of the world that will last for ever

It is a distinctive feature of the Indian religious and philosophical systems that they do not believe in a creation out of nothing in a world process that happens but once and in an ultimate state of bliss which will never end According to the Jains and to some Mimamsakas the world is without beginning and without end according to Hindus and Buddhists, there are innumerable worlds which are produced and again destroyed, so that there is a cycle of creation and annihilation which has gone on since time immemorial Here too the cosmos as a whole has ever existed and will always exist On our earth there is also a continuous succession of good and evil ages There will never be a period of absolute perfection enduring for eternity For this reason Indian philosophers never cherished hopes of a final and everlasting state of beatitude to come The individual soul may reach perfection undergoing the purgatory of many births but the world itself is not changed by this for the number of living beings to be born and to die because of their *karma*, is infinite The Indian idea of *yugas kalpas avasarpinis* and *utsarpinis*, etc reminds one of Oswald Spengler s theory propounded in the *Decline of the*

West every civilization is like a plant it has its origin its time of blossoming its decay and its annihilation When it has passed, another kind of civilization may take its place

Because of these divergent views on the destiny of the world and of mankind the importance ascribed to history is quite different among the Hindus and among peoples brought up to believe in Islam or Christianity Because history does not repeat itself and everything that happens is a unique event on the path of time from creation to perfection it is worth while to write it down and to fix exactly the year when it happened Therefore Christian and Moslem scholars have always been much interested in historical dates and facts

In India on the other hand the pundits have never attached any importance to these matters In the everlasting cycle of time and in the endless succession of reincarnations it is quite meaningless to know when something occurred only the fact itself and its moral implications are important It is for this reason that we do not know when the Indian texts were composed and are equally at a loss concerning the dates of the great Indian poets and philosophers like Kalidasa, Shankara or Ramananda because of the inexactitude of tradition and the conflicting views of Indian writers

The difference between Western and Indian ideas in this respect may be illustrated by the following simile the Westerners see everything through a sort of magnifying glass or as in a slow motion picture while the Hindus see it *sub specie aeternitatis* It is evident that both ways of seeing are one sided one has to be complemented by the other We may quote in this respect a verse of the celebrated German mystic Jacob Boehme who wrote

> *Wem Ewigkeit wie Zeit und Zeit wie Ewigkeit*
> *Der ist befreit von allen Streit* [1]

After these remarks on the gradual progress of the individual and the conceptions of a gradual progress of humanity as a whole let us turn now to our third and last theme is any gradual progress to be discerned in the veracity of the many religious and philosophical doctrines to which the different peoples of the earth have adhered?

[1] He to whom eternity is [illegible] time and time [illegible] eternity is freed from all strife

According to modern science our earth has an age of 2,000 millions of years the human race is said to have existed for 600,000 years and our knowledge of human history covers a space of time not exceeding 6,000 years It is known that during this time man has embraced very different forms of belief till he reached the present state, where five great religions with millions of adherents and some lesser religions, claim 90 per cent of the population of the globe, estimated today at 2 400 millions It is comprehensible that every religion or philosophy or every sect, denomination or school thinks itself in the possession of the entire truth, and yet they may be asked to explain two facts

1 That today only a minority of the human race professes belief in any particular church sect or school
2 That the greater part of the 600 000 years of human life have passed without the existence of present day religions and philosophies

The view generally put forward by dogmatic religions is that other forms are, so to speak preparatory stepping stones leading to the truth Thus Christian philosophers speak of the original primeval monotheistic revelation given to all peoples and thereafter enriched by the special revelations of the Old and New Testaments The other religions are said to contain a germ of truth but this nucleus is mixed up with ideas produced by the imperfection of human understanding or by degenerative tendencies to which humanity fell a prey In a similar way Hindu and Buddhist sects like the *Shaiva siddhanta* or the *Shingon* school try to show that the doctrines of all other religious communities are substrata of the universal truth through which man may pass during his reincarnation till he reaches the final goal The idea that there is an ascending scale of religious and philosophical systems has also been propounded by European philosophers like Hegel and Eduard von Hartmann and by Indian metaphysicians like Madhava in his *Sarvadarshanasangraha*

In a secularized way we meet similar ideas in modern Positivism according to August Comte the human race considered as a great organism, must pass through the stages of theology and metaphysics till it reaches the scientific or positive stage of which Comte is the prophet In the first of these stages men attribute the phenomena of the world to the

actions of gods moved by human passions, in the second stage conceptual entities take the place of divine wills and in the third stage man contents himself with discovering the order in which events occur and trying to give a scientific interpretation of them All these attempts to arrange the teachings of the different systems agree more or less that there is a truth common to all mankind, that this truth is already known and that it is to be expected that after a certain time the majority of the human race will individually or collectively adhere to it

Many Indian thinkers take another view According to them there is no hierarchy of systems but every teaching is an adequate expression of the spiritual needs of an individual Just as the varied tastes of men of different countries climates extractions age and intelligence require different types of food and clothing with nobody expecting uniformity in this respect so also the religious and philosophical views of men are conditioned by a multitude of factors and it is neither to be expected nor even to be hoped that they will ever agree in this matter

When Mahatma Gandhi spoke to me on religious questions he said that the multiplicity of religious and philosophical opinions is not only a fact but that it is also a blessing because every metaphysical thought is only an imperfect interpretation of the world and of the transcendent which is beyond it In a famous simile Buddha illustrated this truth by comparing the different individual views of reality with the blind men of Shravasti who tried to explain what an elephant was As each of them was able to touch only a part of the animal s body their views differed very much the correct comprehensions of reality would only be possible for a being that had freed itself from the natural blindness innate in man This parable had an enormous success for we find it not only in India with the Jains and the Shaivas but also with Mohammedan mystics like Al Ghazzali Sanar and Jalal ud-din Rumi and even in modern Western textbooks as in E S Robinson s *Readings in General Psychology* Since time immemorial every system of dogmatics has been a compound of error and truth because the transcendent lies beyond the capacity of men to express it It is therefore not the outer form or intellectual garb which is of importance but only what man makes of it to become wiser and better

Nagarjuna and Shankara were aware of this when they distinguished two kinds of truth the provisional *samvriti satya* or *vyavahara satya* and the higher or *paramartha satya* The former embraces all systems which try to decipher the riddles of the universe by the help of logic in inference, tradition and revelation the latter can be realized only by meditation, to which man may resort by gradual progress

The concept that there are two kinds of truth which like the two storeys of a big building of thought, lie one above the other, has its counterpart in Western philosophy in the philosophy of Immanuel Kant For according to the *Critique of Pure Reason*, the ideas of the dogmatics are only ideas to regulate our reason, heuristic fictions, symbols of an unknown and inscrutable reality of which we are unable to know what it is in itself and of which we can only know what it means to us

The East and the Problems of Education

by

HUMAYUN KABIR

I

BEFORE we can answer the question as to whether there is any absolute distinction between East and West in their concept of man or philosophy of education we must try to understand what we mean by East and West Obviously the distinction is in terms of geography but even geographically the terms East and West are and must be, relative in a global world Every region of the world is both East and West, depending upon the location of the person who refers to it The description of Asia as East, and Europe as West dates back from the time when men thought of the world as flat and limited The popular description of philosophies developed in Asia as Eastern and of those in Europe as Western is a relic of the same habit of thought

The use of the plural in referring to the philosophies that developed in Asia is a recognition of the great variety of such systems The philosophical concepts that developed in China are often different from those that developed in India or Western Asia Each region developed systems that have affiliations, parallelisms and contrasts Let alone an area so vast as Asia Indian philosophy includes systems which hold that the Brahman alone is real and others for which sense experience is the only reality Sankara and Carvaka have each a place in any history of Indian philosophy though this fact is not always remembered

For various reasons, into which we need not enter many scholars have come to regard Vedanta as the main type of Indian philosophy and of the many interpretations of Vedanta the one associated with the name of Sankara as the only valid one Consequently to many scholars both Indian and foreign Sankara s views have been regarded as Indian *in excelsis* At the same time Sankara s position has not always

been correctly understood Even today critics are not agreed about what Sankara meant by the concept of *maya* Is *maya* illusion or mystery? What again was Sankara s relation to Buddhist metaphysics? Did he not, with the Buddhists, deny the transcendental reality of the world as we know it? Many today regard Sankara as a confirmed critic of Buddhist thought but in his own age he was often held to be a dis guised Buddhist

Even if we accept the conventional view about Sankara's philosophy, there are other orthodox Indian schools which give greater recognition to the reality of the individual and his acts In addition to the six orthodox schools there are many heterodox schools of varying degrees of insight and influence These systems—orthodox and heterodox—exhibit among them almost all possible variations of human thought Furthermore, divergences between them are at times wider than those between a particular Indian and a particular European system

The same remarks apply to the concept of man put forward by different philosophers who have lived in what we call the West Even within the comparatively limited field of Greek philosophy, the attitude of Heraclitus and Parmenides to reality and man are sharply opposed Human thought in Europe as elsewhere exhibits two main but contrary atti tudes Some thinkers have stressed permanence and regarded the flow of things as only a process distorting the hidden reality Others have regarded change as fundamental and identified process itself with reality Philosophers have also differed about the importance of the respective contributions of sense and understanding to our knowledge To some, the essence of man is his rationality Others have identified man with the stream of sense perceptions Naturally, their concept of man has differed These differences however cut across geographical barriers We find exponents of either school in both Asia and Europe Just as there is no single concept of man which is typically Asian there is none which is specifically and exclusively European

It is true that the Greeks had divided mankind into the Hellenes and the barbarians Indians drew a similar distinc tion between the Aryans and the Mlecchas and the Hebrews between the Jew and the Gentile The self chosen race had in

each case a sense of its own superiority mixed with a feeling of patronising contempt for others It is however doubtful if the ancient world had articulated the distinction as one be tween East and West This latter distinction is a later growth, and is largely the result of military superiority which European nations achieved after the Renaissance through the applica tion of science to the art of warfare

Military superiority led to political domination by Europe in particular by the nations of Western Europe and encour aged the growth of a superiority complex that at times degen erated into arrogance The Greeks, in spite of the sense of their own importance recognized the superiority of the Egyptians and some other Eastern nations in certain fields Hindus had similarly acknowledged the contribution of the Greeks to sculpture military science and astronomy Euro peans till the Renaissance had admitted the excellence of the Saracens in various arts and sciences Western Europeans of the post Renaissance period however developed a tendency—sometimes formulated but more often tacitly assumed—to regard all human excellence as their special prerogative

Europe, Africa and Asia—and these constituted the then known world—influenced one another from the beginning of recorded history What is today described as the West is based mainly on a synthesis of Greek and Hebraic elements while the East contains traces of Hellenic art as well as the impact of modern science If a distinction is to be drawn at all between East and West it would not perhaps be incorrect to say that the spiritual equipment of the West was furnished largely by the East while the intellectual content of the East was partly derived from Western sources Christianity which has profoundly influenced Europe, originated in Asia but returned there in a European garb The only valid conclusion is that no concept of man can be described as exclusively Eastern or Western In other words the world of philosophy cannot be divided into water tight cultural blocks

II

One may well ask if this be so why should men have ever thought of East and West as distinct if not contrary manifesta tions of the human spirit? One answer is that human thought

is largely influenced by environment, and this differs in different regions Man does not think in a vacuum The content of his thought must be derived from his experience and his experience will be largely shaped by his natural and human environment To take one example the desert, with its vast brooding skies and the vast unbroken span below, tends to blur all distinctions and to impress upon the mind a sense of the unity of the universe From this sense of unity it is only a step to think of one God and one Law This helps to explain why the most intense expression of monotheism is found in the semitic religions

Though we do not always see the connexion the forms of production and the relation of the different classes to the productive forces, also influence the prevalent thought of a community The longer one particular social form lasts the stronger is its impact on the mentality of the people It is *common experience that men following the same avocation* develop a similar mentality Agricultural communities all over the world are inclined to be tribal and parochial The unit of life is the village community In such a social setting, the individual s claim to independent life tends to be ignored On the other hand social co-operation is restricted to the members of the village group The individual rarely if ever thinks of his relation to his country or his nation His loyalty is more to the family or the clan than to the nation or the country India with her dominantly agricultural economy of 4 000 years or more, offers an example of how this principle works The form of her economic life, with its emphasis on the village community, retarded the growth of individualism and nationalism alike

Let us take another example of the way in which economic organization influences outlook on life The peasant—especially before the discoveries of science and technology—depended for his prosperity on factors over which he had no control He could prevent neither drought nor excess of rain A peasant economy thus fostered an attitude of fatalism By contrast, communities which were commercial or industrial developed in the individual a more self reliant, empirical and adventurous outlook We find such differences between agricultural and commercial communities in both Asia and Europe Medieval Europe, which was largely agricultural, was nearer

spirit to contemporary agricultural communities of Asia than to the industrial Europe of today Here we have another that differences in outlook between peoples are due not so much to geographical location as to the stage of their social and economic development

The influence of the social structure can be traced in some of man s most abstruse speculative efforts It is sometimes said that what distinguishes the Indian concept of man is belief in the doctrines of *Karma* and transmigration or rebirth These are not two doctrines, but two formulations of one fundamental principle This principle is the application of the law of causality to human destiny It holds that what happens to man is neither accidental nor due to the vagaries of any non human factor Each man is responsible for his own fate As he has sown so has he reaped till now and so will he reap in the future The consequences of his action are not exhausted in one life and hence he must be born again and again The doctrine of *Karma* and rebirth is thus an attempt to assert man s independence of God or any other superhuman agency

We may find parallels to the doctrine elsewhere Some elements in the thought of Socrates present a close analogy The doctrine as fully articulated is however peculiar to India One reason why it flourished here may be found in the organization of Indian society as it unfolded itself in the wake of the Aryan immigration The Aryans came to India in driblets and faced a people or peoples who were inferior in a military sense but perhaps their equal in other respects The Aryans conquered and subjugated them but allowed them to survive as inferior classes in the social hierarchy Caste developed out of this social stratification Inequality was perpetuated by giving it an *institutional* basis We may condemn caste from a humanitarian point of view, but historically we must recognize that it offered the conquered though under conditions of privation and disability a chance to survive

The survival of the conquered under conditions of humiliation and misery posed difficult social problems A hierarchical society always tends to concentrate privilege at the top The denial of rights to the conquered leads in course of time to the denial of privilege to the less fortunate among the conquerors Such societies must therefore constantly face the risk of revolt

by the underprivileged who constitute the majority Such risks are minimized if the majority are persuaded that (a) they are themselves responsible for their sad plight, and (b) can hope to improve their status in an after life by patient sub mission to present misery The doctrine of *Karma* satisfied both these conditions It inculcates in the mind of the majority the belief that their misery is due to sins in a former life It offers them the hope of future betterment through present performance of allotted tasks

The doctrine need not be and most probably is not a con scious attempt to justify existing social practice but there is no doubt that it fitted in with the requirements of the dominating class *in society Such a class by the very fact of its status tends* to be more intelligent and enterprising Its beliefs tend to set the tone for the whole of society It is therefore not surprising that principles acceptable to the privileged class should in course of time determine the outlook of the society as a whole

The use of gunpowder in warfare offers an example of how a scientific discovery influences the course of social development One of the bases of European feudalism was the superior military power of the knight With his coat of arms, he was largely immune from the attack of the common foot soldier till gunpowder destroyed his immunity Gunpowder thus directly contributed to the overthrow of the feudal sys tem and indirectly helped in the growth of a spirit of demo cracy by establishing equality of risk among all combatants The decay of feudal institutions created conditions for the emergence of new ideas more suited to the new social set up

The conclusion then is that differences in the concept of man in different countries or times are not intrinsic, but are functions of differences in their social organization and de velopment That such differences should come to be regarded as intrinsic or immutable can be explained only by man s tendency to identify a thing with its name Nominalism is no longer a fashionable mode of thought, but its influence persists in unexpected ways Without names man would not be able to use concepts and without concepts he could not organize his experience Human energy is limited while the objects that claim man s attention are many He must therefore classify and label so that he may bring an unlimited number of instances under a single rule Since he can do so only by

the use of names, he thinks that he has understood a thing when he is able to name it.

It is not surprising therefore that the name is often taken to be the reality. In ancient forms of philosophy, whether Eastern or Western, we find a tribute to the power of words in phrases which identify the word—*sabda* or *logos*—with the reality itself. In course of time, men discovered that the value of words is mainly instrumental, but the power of names could not be so easily shaken. If we want proof of this, we need only refer to the slogans which dominate human attitudes and actions.

The fact that ancient societies developed in isolation from one another helped to perpetuate the nominalist fallacy. Owing to difficulties of communication, societies in different regions were often unaware of one another's existence. Absence of contacts made the co-existence of different stages of civilization, and hence of different kinds of world outlook, possible. It was also natural that these outlooks should be described in terms of the regions in which they flourished. Once an outlook or attitude was given a geographical label, it was an easy step to identify it with the region.

III

On general grounds we may therefore say that no concept of man is peculiarly Eastern or Western. We come to the same conclusion if we consider philosophical traditions which are regarded as characteristically Eastern or Western. It is often said that the Eastern philosopher tends to give an important if not the central role to intuition as a way of knowledge, while the Western philosopher is more inclined to bring all cognitive claims to the test of rational and empirical evidence. This statement is true only with large qualifications. No Indian school of systematic philosophy—whether orthodox or heterodox—accepts a theory which fails to satisfy the test of logic. Some of the greatest names in Western philosophy, such as Plato and Kant, give intuition a central place in their philosophical systems. Again, it is said that the Western philosopher is more concerned with *thinking about* and the Eastern with *realization of* reality. This may be true in some cases, but there are also Eastern philosophers whose main concern is to *think about* and Western philosophers who regard knowledge

as only a *means to the realization* of reality Similarly, if there are Eastern philosophers who regard the highest knowledge as not amenable to verbal expression and communication, there are also Western philosophers who like Wittgenstein, regard true knowledge as inexpressible

The degree of control over the force of nature has also influenced man s outlook in different countries or ages In all primitive societies man is subject to forces which he can neither understand nor control Such societies tend to think of man as a plaything of fate Agricultural societies show some increase in man s control over nature, and bring with it an increasing sense of man s importance Without the art of irrigation agricultural man was still subject to the vagaries of the weather and hence fatalism was an important element in his mental attitude With the advance of scientific knowledge he gains in power over nature, and develops greater self assurance He is no longer content to be a victim of fate, but seeks to become master of his destiny There is a corresponding change in his attitude This is due to a change in the state of his knowledge but in course of time comes to be regarded as an intrinsic characteristic of the society to which he belongs

Even man s discontent with things as they are varies with changes in the degree and extent of his power over nature Driven by an urge for progress he always seeks to improve on the present When his control over the surrounding world was limited and he understood little of the secrets of nature his discontent often expressed itself in a mood of philosophical pessimism Hebrew prophets and Hindu sages spoke alike of the transience of life and the impermanence of earthly pomp and glory With the progress of scientific knowledge the same divine discontent found a different expression among the philosophers and scientists of Renaissance Europe Their dissatisfaction with the existing world led to an attempt to wrest the inmost secrets from nature and mould the world nearer to the heart s desire

This attempt to master nature released hidden energies which enabled a handful of Western Europeans to dominate the world for more than two centuries This domination was not only in the political field but also in all activities which we loosely describe as spiritual Europe s adventurousness and initiative, her faith in human reason, her quest for truth and

her endeavour to alleviate suffering wherever it exists are all based upon the power given by superior knowledge These achievements are a proud heritage for all men If, then in recent times there has been a revolt against European leader ship, this has been on account of the tendency to make superior knowledge the basis of political domination and racial exclu siveness It must however be pointed out that the revolt itself owes much to the work of some of the finest spirits among the European peoples

It is thus only in recent centuries that we find a difference in outlook, temper and energy of man in Europe and elsewhere To conclude from this that there are intrinsic differ ences between East and West is not justified The eclipse of non European countries was due to their dependence on agricul ture and their lack of scientific knowledge and technical know how The spread of scientific knowledge is however tending to obliterate these and other disparities Regions which were isolated, and developed along different lines have now been brought close to one another in space and time Such proximity brings with it the risk of conflict if not disaster unless gross inequalities between individuals and societies are removed by the establishment of a common outlook and common standards

The physical conditions for such a development have been established In the past man s knowledge of the world was limited and attempts at establishment of unity were also limited in nature and scope This was generally between adjoining regions and confined to the elite who found a basis of co operation in common intellectual and spiritual interests Today the co-operation must be among all men in all regions By the middle of the nineteenth century the known world and the geographic world were co-extensive The conquests of science made men in distant regions one another s neighbours Political and economic relations have thus been established between peoples who have no consciousness of common ties Science has at the same time placed in their hands a power that is capable of destroying the world if not wisely used Increasing power with growing unification of the world makes man s action and its repercussions literally global Unity to be effective must therefore also be global The modern world must prosper or perish as one unit.

Technologically, industrially and economically, the world has been unified through the achievements of science Psychologically, emotionally and politically man has not however yet attained unity Intellectually, he recognizes that he cannot harm others without harming himself and that when he does good to others he does himself good Intellectual recognition has not however been accompanied by a comparable change in his conduct He still fights his fellows in the name of human reason and the social good

This paradox is due to the fact that his knowledge of the world outside is not matched by his knowledge of the inner self Passions sweep over him that he cannot understand When in company with his fellows, he often behaves in a way unimaginable to himself when acting alone The mass hysteria which sweeps over him reveals in his nature a potentiality for evil of which he was quite unaware before the event Never has the realization been so poignant that there are unplumbed depths in human nature that man can ignore only at his peril

The nineteenth century was the age of militant rationalism The triumphs of science led men to believe that the education of the intellect would lead to a change of the heart and allow all men to meet on a common level of rationality That hope has not been realized This has induced in some a curious sense of helplessness and an attitude of fatalism reminiscent of days when man had no control over the forces of nature Increasing knowledge of external nature helped man to overcome his primitive fatalism It may be that increasing knowledge of man's inner nature will help him to conquer the fatalism of the modern age

IV

Education seeks to give the individual knowledge of himself, his fellows and his environment Knowledge of the inner as well as the outer world is thus a function of education Since man cannot live by himself the aim of all systems of education, whether of East or West is to help individuals become better members of their community Systems of education have therefore varied with differences in social organization and have placed a greater emphasis on one or other element in human nature

Differences that are at first only in emphasis lead in course of time to the neglect of some vital element in man s nature To take one example In ancient India, education sought to achieve the four fold goals of *Karma*, *Artha*, *Dharma* and *Moksha* So long as Indian society was healthy and vital all the four aims had their due importance As the nation s vigour declined there was a shift in emphasis, and gradually an ascetic spirit became dominant in society It sought to glorify the spirit at the expense of achievements on the worldly plane As the social outlook changed the character of Indian educa tion also changed The emphasis shifted from an active to a contemplative life Conformity to traditions and reverence for authority were regarded as higher values than intellectual curiosity and independence of outlook Submissiveness and contentment were dignified as spiritual values forgetful of the fact that they are sometimes indistinguishable from passivity and quiescence One curious result of this so called spirituality is seen in a tendency to withdraw within oneself and shun all manifestations of external activity As a result Indian educa tion tended to glorify exercise of the intellect—perhaps not even of the intellect but of the memory—at the cost of the other human faculties Emphasis on the mental induced an attitude of indifference to if not contempt for all manual work

The experience of Europe offers a contrary example of how undue stress on one element leads to a distorted view of education Plato believed that education should lead to a harmonious development of mind and body and placed equal emphasis on mathematics music and gymnastics as educative media This ideal was never consciously challenged but in course of time the emphasis shifted to the development of the intellect The astonishing triumphs of science since the be ginning of the Renaissance encouraged Europe to apply the methods of scientific enquiry to the problems of human per sonality, without enquiring whether such methods are always applicable The essence of the scientific method is its indiffer ence to the particular instance The essence of personality is that each individual is a distinct centre of self-consciousness

A theory of education formulated under the influence of science tended to treat the individual as an instance of a law or a unit of a standard series Human society was regarded as a conglomeration of such units Social relations were explained

on the analogy of physics It was even thought that individuals and their contractual relations corresponded to atoms and their gravitational relations From this it was deduced that competition was the principle governing social progress It was held that if each individual pursued his own ends, the ends of society would be served automatically Social good was regarded as the resultant of the pursuit of enlightened self interest by the individual

While the aim of science is to establish universal laws, these are thought to be based on the facts of concrete experience Education in Europe was influenced by both the rationalist impulse and the practical bias of science The rationalist impulse expressed itself in an emphasis on abstract apprehension The practical bias is seen in the constant effort to improve the material conditions of life This humanitarian element in the European concept of education was reinforced by the growth of the biological sciences As a result of these developments, theories of social contract were gradually replaced by the concept of society as an organism

The recognition of the organic character of society did not however have an immediate influence upon the principles or methods of education Even today we do not fully recognize that co-operation has been as potent a factor as competition in man s survival An organic conception of society has led to a change in our concept of the individual and has helped us to appreciate his infinite complexity It is therefore increasingly recognized that education which aims at the development of personality must allow for the unfolding not only of his intellect but also of his feelings and imagination

V

We therefore need a reorganization of education which will cater to the needs of *homo sapiens* as well as *homo faber* This does not mean that educational methods and standards must be the same for all It only means that they must be comparable The application of science and technology to the field of production has proved that the prosperity of nations depends upon the state of their knowledge It has at the same time created conditions in which the good things of life can be made available to all Mechanical devices can remove much of the

drudgery of life The world can today look forward to an economy of plenty in place of the economy of want which has ruled till now Among individuals the rich and the poor do not make good friends This is equally true of nations Comparable prosperity of different nations is therefore a condition of international understanding and the key to such prosperity lies in comparable educational standards

The condensation of the world as a result of advance in technology thus demands a greater approximation in the ideals and methods of education Such approximation must not however be at the cost of suppressing individual variations and needs Within national systems of education, we have realized the need to provide more diversified courses to suit the tastes and aptitudes of individual pupils It is equally necessary to provide for diversity among different national systems While scientific progress tends to reduce economic and political differences among peoples it encourages greater diversity in the cultural field by releasing energies from the bare struggle for existence The greater the margin above want the more varied are man s tastes and interests Scientific progress does not therefore connote standardization of culture and still less cultural imperialism All that we need and ought to strive for, is to ensure that the values achieved by man in the course of his long history are available to all

The lessons of history impress upon us that to be fully effective education must be for the whole man It must offer scope for the development simultaneously and in proper balance of his body and mind of his intellect and his imagination This is what educational reformers have been trying to do for the last 100 years or more Many Western educationists have pointed out the importance of activity as an element in training the very young Theories which identified education with the imparting of information have been and are yielding place to the idea of education as an active drawing out of the best in the individual About 50 years ago Tagore said that true education must allow the child freedom to develop in close association with nature Gandhi sought to give to the activity of the child a socially useful end All these experiments Eastern and Western stress that education should not be regarded as a mere intellectual discipline but a discipline of the whole man

In the past, education has sometimes ignored the relation of the individual to society This made education abstract and comparatively unreal It also failed to evoke the interest of the young A concrete situation is more easily grasped by a child and helps to bring out his qualities of feeling, imagination and thought When dealing with abstract entities the child often falls back on his power of memorizing That is why the new educational experiments in the West, and those of Tagore and Gandhi in India lay such emphasis upon activity Learning by doing arouses the child s interest and also makes him realize the consequence of what he does

Society must from its nature, be served by different individuals with different abilities and different functions Emphasis on the social character of education (a) helps to develop a spirit of co operation (b) leads to the recognition that differences in function cannot be equated with differences in value and importance and (c) softens the rigid distinction between intellectual and manual discipline Technical education was once regarded as a craft, or at most an acquisition of skill in a particular trade or industry Today, technical education is being recognized as education in the fullest sense of the term provided the social significance of the craft is kept in view In a country like India this new conception of education is bringing a new recognition of the dignity of labour

New education must also emphasize as perhaps never before the intimate inter relation of individual societies to the larger society of mankind Never before have nations been brought so close to one another Today whatever happens in any part of the globe immediately affects all A nation can ignore what happens outside its borders only at its peril Gone are the days when a society or nation could withdraw within its own frontiers and pursue with greater or less success the course of its own development Education throughout the world must therefore pay increasing importance to international affairs

Men and women of one country must seek to know and understand the problems of their fellows in other countries The first step towards this is the removal of misconceptions One source of misconception is the concept of race Anthropology tells us that there are no innate differences between races and many anthropologists regard the very concept of race as

a myth All anthropologists however agree that differences that have evolved over long stretches of time in response to different requirements in the situation have led to the emergence of distinct ethnic groups Two things follow from this So-called racial differences are not absolute or immutable and can and do change in course of time On the other hand any attempt to deny or suppress them abruptly is fraught with grave risks

Another source of misunderstanding is defective teaching of history and geography Till now they have generally been taught from a narrow national point of view History has often meant a glorification of one s own country Geography has tended to regard one s own country as the centre of the world This has often been accompanied by a corresponding under estimate of other peoples or lands If we are to avoid the danger implicit in such practice, we must revise our conception of history and geography History must no longer mean a mere knowledge of the political relations of different peoples which are in any case full of the record of conflict and struggle We must now recognize that more fundamental than the tale of wars is the story of the long and far flung co-operation by which man has attained his present state No one knows who discovered fire but its use is one of the basic facts of human life The names of the men who discovered paper and printing are unknown but the results of their discoveries belong to the common inheritance of man We have no knowledge of the individual or the people who first discovered the art of agriculture or of navigation or of transport But who can deny that these discoveries have made a far greater difference to the quality of human life than the most far flung conquests of the most famous kings?

In one of his most exquisite stories Anatole France tells us how Pontius Pilate dwelt on many cherished memories of his governorship of Judea but could not remember the name of Jesus an insignificant visionary who had been crucified to appease the orthodox Jews! This is perhaps an extreme case but can we deny that we have generally failed to give proper value to the achievements of peace? There are thousands of instances where a discovery—by accident or design—by some individual or group has led to a permanent enrichment of the human heritage and yet found no mention in the annals of

man Once an insight has been achieved, it becomes in course of time the possession of all minds Once a technique has been discovered, it improves the quality and volume of production throughout the world Such achievements and discoveries constitute the real story of man s co operation with his fellows and must form the basic material of history

Our knowledge of the nature of man is still inadequate but we have repeatedly seen how ideas influence men and shape the course of history The problem of education in the modern world is to develop in men attitudes which will lead them to work for the common good They will not, perhaps cannot, do so unless they are at peace within themselves There can be no integrated society without integrated individuals and no peace for the world without integrated societies Individual and social integration depends upon the formulation of com mon ideals It is only through education that these ideals can become a part of the mental make up of all men

Even in a well knit and homogeneous community individ uals differ from one another widely Such differences do not however lead to conflict as there are certain assumptions which are common to all members of that group Societies must evolve a similar basis of common ideals They can be indicated only in very general terms but must among others include the following values (a) Physical well being for all, (b) economic sufficiency guaranteeing the conditions of survi val to all (c) freedom from domination in economic political, social or cultural matters, and (d) the freedom of each individ ual or group to develop to its full capacity without infringing upon the rights of others

Since human attitudes and aptitudes are not immutable and fixed they can be changed through a proper educative pro cess Education can therefore create the conditions for, and serve as the medium of, co-operation between the prevalent cultures of the world In addition education must in the mod ern world serve as an agent for bringing about progress without violence There is no society which is not in a state of continual change External events and internal processes are continually transforming the character and composition of individuals as well as societies The vitality of an individual or a society can best be measured by its capacity to respond to external and internal stimuli To live is to change Too abrupt

a change can however lead to disruption of unity In such cases individuals and societies not only change but disintegrate

It is the function of education to develop an attitude which will facilitate progress without violent upheavals or abrupt breaks In the past, man s inheritance was often limited to the achievements of his own forebears Today the unification of the world has made him the inheritor of all that has happened to man in every age and clime He is able today to survey the rise and fall of societies through centuries and learn from history that willing acceptance of change is a condition not only of progress but of survival Education in the modern world must therefore foster in man a spirit of toleration and resilience toleration which seeks to integrate all values achieved by all civilizations into one common heritage for man, and resilience which enables him to meet the challenge of each new situation with a new and creative response

The Friction and Fusion of Domestic and Foreign Ideas in the Formation of Japanese Culture

by

YENSHO KANAKURA

IF we look upon the history of Japanese culture lasting for more than 10 centuries we can clearly perceive that its remarkable development has always been due to the strong stimulus given by the introduction of foreign cultures But this development of Japanese culture has by no means trodden a smooth path without vicissitude Every imported foreign idea has conflicted with the Japanese temperament When two of these opposing forces have attained a certain balance there has grown a new basic idea of culture And yet again, this newly born culture has been shaken by another imported culture, and a higher synthesis has been once more required This repetition of strife and reconciliation is the fundamental characteristic of the formation of Japanese culture and this too, is one of the difficult problems now facing Japan

Taking the motive of its development in the acceptance and digestion of foreign cultures, Japanese culture differs from those of India and China although it belongs to the same sphere of the Orient India and China had their own civiliza tions highly developed in ancient times and exerted a broad influence upon other races They took too great a pride in their own cultures to accept open heartedly any heterogeneous one Even when these countries were obliged to set themselves under the political control of other races the culture of the conqueror was finally assimilated to that of the conquered

In Japan the situation is quite different As you will see more fully in the following pages ancient Japan had no highly developed culture but a primitive one nurtured by the im ported Chinese and Indian cultures In spite of its changes and vicissitudes it has generally accepted and digested other systems and cultures, Oriental and Occidental whenever they were introduced into Japan

Thus from ancient times the Japanese have taken in various cultures of the East and the West successively, and among them those of India and China at least have been almost completely digested their extracted essences being adapted to the Japanese national character In other words, those two cultures, metamorphosed, became the creative element of Japanese culture

At this critical juncture when the fusion and intermixture of the East and the West is a great problem, and there is a strong demand throughout all the nations on earth for harmony between, or reconciliation of, the two opposing worlds, does it not suggest to other nations a partial solution to the problem that they reflect upon this process of the assimilation and development of foreign cultures in Japan? Granted that the current problem cannot be discussed in the same light as culture, perhaps a brief review of the development of Japanese culture might constitute an experimental test tube report on some urgent present day problems

Primitive religion in Japan was based on nature worship and ancestor worship, with a tendency towards animism and a strong tint of Shamanism At its earliest stage religion was not distinguished from administration Later, a simple myth making the imperial household as its head family of the race was formed while the political unity of the country was in the process of being built up with the emperor as its centre

In the latter half of the third century Chinese culture was introduced into Japan through Korea in the form of Confucianism and Buddhism With the introduction of Confucianism people began to pursue knowledge and to learn letters for the first time, and they awoke to a sense of ethical norm

The introduction of Buddhism through Korea came a little later than that of Confucianism, but it was diffused among the court and nobles in a very short time This was the underlying cause of the rise of two powerful sects which waged a bloody struggle for supremacy—one the progressive pro-Buddhist and the other the conservative anti Buddhist Finally progressivism won and a brilliant flourish of culture resulted led by the famous Shotoku Taishi (Crown Prince Shôtoku)

With the importation of Buddhism the Japanese for the first time acquired religion in the true sense of the word their ancient religion Shintoism could not be said to be such, since

it had no creed and did not preach a future life The highest forms of art were brought in from China together with Bud dhism The so-called fine arts of the Suiko dynasty deserve our appreciation even today Thus the Japanese people came to know an ideal world beyond reality—a world of beauty above the practical one Shotoku Taishi (A D 574 621) annotated the Sutras of Mahayana thus giving a guide to the future of Japanese Buddhism, and enacted the 17 article Constitution, with peace as his political ideal He was the first and greatest statesman Japan has ever produced as a patron of culture

Some 90 years after the coming of Buddhism, a great political reform took place Its leaders were the students of Confucianism and the conservative followers of Shintoism As worshippers of Chinese civilization, they strove for national centralization along the lines of the institutions of *T ang* Many students were sent to *T ang* to study and bring back with them various kinds of learning which resulted in a magnificent efflorescence of culture in the Nara dynasty (A D 708 780) At this time Buddhism became almost a state religion, the creeds of Hinayana and Mahayana being studied separately Great temples were erected with many wall paintings, sculptures etc and the influence of these original designs can be traced today in the remote areas of Central Asia, Persia Greece, and Rome In literature the Mannyoshû , an anthology of poems and songs peculiar to Japan was compiled, displaying a sublime and unsophisticated national spirit

At the beginning of the next period Heian dynasty (A D 794 1191) two priests Saicho and Kûkai went over to T'ang On returning to Japan they founded two sects of Buddhism Tendai and Shingon respectively Saicho s Tendai sect was a new synthesis of the systems of four Buddhist sects in China, based on his own experiences Kûkai made esoteric Buddhism the first independent sect interpreting the universe itself as the *dharma kâya* of the Mahavairocana, and teaching the theory that our body can immediately realize the *dharma kâya* of the Vairocana These two sects unlike the academic Buddhism of the Nara dynasty, contributed directly to the progress of Japanese culture in that they had secular tenden cies and social merits In this period also Kana letters were invented and widely used The *Tales of Genji* a literary

masterpiece, in which are interwoven the pessimistic views of life based on Buddhism were the product of this period Generally speaking, the main characteristic of the current view of the world was aesthetic eudemonism and naturalism affirmative of this life pantheistic Buddhism also played a part in affirming such realism through the medium of magnificent Buddhist rituals composed of incantations and prayers

However, the aristocratic culture of the Heian dynasty which attained the very height of prosperity revealed signs of gradual corruption Insurrections and rebellions followed successively, social insecurity and unrest increased Consequently, pessimistic ideas denying this world gradually became popular Thus we come to the Kamakura era

In the Kamakura era (A D 1192 1333) under military government the rise of Bushido or chivalry and the establishment of the new Buddhism were the most notable developments from the point of view of cultural history Bushido, or the customs naturally formed and exercised among the samurais—a newly risen class and the bearers of culture in this period—attached special value to loyalty, self denial, and temperance Characteristically it attached great importance to steadfastness of mind and strong will despising every enjoyment Bushido was primarily a doctrine based on practical experiences, but as it absorbed Confucianism and Buddhism, particularly the culture of the *Zen* cult it became purer

The new Buddhism which followed was merely a reformation resulting from the secular degradation of the old Buddhism and from social insecurity Although they have always inherited the tradition of Buddhism in India and China these new Buddhist sects based on the religious experiences of each Japanese founder are quite different in their character from the older ones This new religion might be called the true Japanese Buddhism for at this period great Buddhist priests —Honen Shinran Eisai Dogen Nichiren etc —appeared one after another and taught new doctrines Contrary to the former Buddhism which had centred around the nobles their goal was to reach the common people and they all gave importance to precise practices rejecting complicated doctrines

Eisai and Dogen went to Sung to study, and introduced the *Zen* sect to Japan In particular Dogen (A D 1200-1253) produced great books founded on his own keen experiences

and profound thinking Even today he is highly esteemed as a great philosopher The *Zen* sect, not depending upon any Buddhist scriptures, teaches that one must return to one s heart, to behold the Buddha nature within oneself, and exert oneself to realize it Its main characteristic consists in an earnest *dhyana*—meditation At this time not only did many Japanese priests visit China for study, but a great number of Chinese *Zen* priests came to Japan to introduce several *Zen* cults and set up various institutions

Honen and Shinran were master and pupil Both of them preached the teaching of the *Jôdo* sect that, through intent faith in Amitabha Buddha one could be reborn in the Buddhist elysium Shinran (A D 1173 1262) intensified his master s teaching and concentrated all Buddhist precepts in the sole penance of praying to Amitabha Buddha His profound consciousness of guilt, and his pure undefiled belief in Buddha s mercifulness had great influence upon many people

The invasion of Yüan in the Kamakura era, encouraged the national consciousness of the people so greatly that it was reflected in a new trend of Shintoism as well as in the writings of Nichiren And this national consciousness, influenced by the new Confucianism of the Sung era, was expressed even more strongly in the Yoshino era (A D 1333 1392)

When we come to the next period the Muromachi era (A D 1392 1568) we notice a new growth of literary accom plishments which are represented by the no plays, the *kyôgen*, and the tea cult In their background lie Shintoism, Bushido and Buddhism The art of tea making in particular, combined with the spirit of the *Zen* sect, symbolizes the culture of this period displaying its quiet plain taste

In the meantime, powerful clans in various parts of the country became influential as the central political power declined, and a renewal of national solidarity was urged Some of the powerful local clans associated directly with the Portu guese, through whom they came into contact with Western culture, and even tried to send their envoys to Europe It was at about this time (A D 1549) that St Francis Xavier intro duced the Roman Catholic Church into Japan The Catholic belief spread throughout the country like wild fire but it was only a temporary phenomenon Soon national unity was

achieved by the Oda and Toyotomi families who were succeeded by the Tokugawa family

The 250 years of the Tokugawa era (A D 1603 1866) was in general a period of seclusionism varying in degree It was an era in which medieval feudalism was centrally established Confucianism was most esteemed in learned circles and the Christian faith was banned At the same time the study of Japanese classics grew gradually, and achieved a system of its own accompanied by a trend towards anti Buddhist agitation On the other hand, Buddhism taking advantage of the current peace, penetrated the mind of the common people more deeply Benevolence and gratitude became the cardinal ideas of the practical morals of the time However the study of Japanese history and Shintoism encouraged the idea of restoration, and the rejection of the Shogunate government which gave impetus to the nation wide cry for direct Imperial rule When the demands of Western countries to open the country for foreign trade became urgent, the Tokugawa Shogunate could no longer cling to seclusionism and finally collapsed yielding to the new era of Meiji

While seclusionism or the national isolation policy of the Tokugawa government surely hindered Japan s progress nevertheless it gave the nation a chance to readjust, reflect upon, and mature its time honoured culture The unique riches of its fine arts industrial arts and literature in that period bear witness to this fact For example we might mention Ukiyoé as a typical representative of the pure Japanese arts produced during the era

Finally, we might consider the period starting from the Meiji era (A D 1869) as the present age It was a great shock for the Japanese long accustomed to feudalism to take up direct and frequent intercourse with modern European countries, the Meiji Restoration being a turning point Yet it is owing partly to its geographical position and partly to a precious sense of nationalism and a genius for adapting foreign institutions that Japan has been able to maintain her independence unlike India and China which have succumbed to exploitation by strong Western colonial powers Thus by following the example of Western art science and administration Japan multiplied its national resources in a short time and rose suddenly as a strong power in the world Nevertheless

it is very doubtful if we, with our long cultivated Oriental mode of thinking, could fully appreciate the European rational spirit Had the Japanese understood this spirit perfectly they surely would not have been involved in the reckless World War II and would have been spared the consequent misery of defeat Here lies an important subject of introspection for the post war Japanese and a valuable hint for their future orientation

In present day Japan in addition to ancient Oriental ideas and religions we have Greek philosophy, German philosophy, American pragmatism French literature, and so on Christian ity alongside Marxism It is not an exaggeration to say that every idea in the world is whirling around us Moreover, there have arisen a great many new religions in post war Japan The most important problem imposed upon Japanese thinkers is how to adjust and embrace these thoughts so that an entirely new outlook on the world can be arrived at Dr Kitaro Nishida (A D 1864 1945), a learned student of Oriental and Occidental ideas set up his own system of philosophy, which, however cannot necessarily be considered as a leading in fluence in post war Japan It remains for a wholesome new culture to be born from the throes before Japan can make its contribution to the welfare of mankind

This is but a very rough summary of the inter relation of Oriental and Occidental ideas which have served as a back ground to the formation of Japanese culture It demonstrates, at least that before heterogeneous thoughts and traditions can be reconciled a very close contact and a considerable lapse of time are necessary The Japanese are primarily flexible of mind keen of intuition, and very tolerant Therefore they have absorbed various ideas and thoughts and digested them well, but in doing so they have spent many years Of course I do not mean to say that they have disregarded their natural progress On the contrary, there has been a strong underlying desire to improve their national culture, by keeping old ideas in harmony with new ones and by uniting them And this respect for harmony is one of the Japanese characteristics from ancient times Moreover, this, backed by the philosophy of Buddhism which teaches the universal equality of men has become an ideal of the Japanese In truth, we have seldom

ousted any foreigners or foreign cultures as a whole because of racial prejudice, though it cannot be denied that a few instances of this occurred, which proved to be against the ideal of peace in the ups and downs of Japanese history The part Japan played in the last World War is one of the greatest blunders she has ever committed However, a close study of Japanese history shows that it was only a rare and temporary digression from the characteristics and ideals peculiar to the Japanese

I believe that real world peace can be attained only by mutual respect for each nation s independence There can be no lasting peace where one race or nation, on premises of racial superiority or inferiority, justifies its own acts but not those of another True conciliation can be realized only in a world where there is no discrimination, except between good and evil Any outlook on the world which consists in regarding *oneself as standing against the other* always *brings the latter* under the former s rule and a distinction arises between the judge and the judged In such a world no complete principle of equality can exist In spite of the fact that many years have elapsed since the liberty and equality of men were first advocated throughout the world and in spite of the fact that it has become a hackneyed motto of modern politicians is it not because of *such an underlying sense of discrimination con* ceiving the self as versus others that even today there are cases of the restraint of liberty and the unequal treatment of men everywhere? Liberty and equality can never be realized merely by an outcry for them We maintain that the new humanism should be established on the view of mankind which postulates that all human beings are equal

National and International Values

by

IBRAHIM MADKOUR

THAT East and West exist is self evident and the differences of geography and climate between the two halves of the world are obvious to all But are we to assume that there are psychological and mental differences as well? That is an assumption sometimes made, as when distinguishing between the analytic or Semitic mind on the one hand, and the synthetic or Aryan mind on the other Renan also spoke of the monotheist instinct characteristic of the Semites, and some people even go so far as to attribute different hereditary psychologies to the various different races asserting for instance, that the yellow races live in the past the black races in the present and the white races in the future Theories such as these, it seems to me, are superficial and extremely risky

Despite all the conflicts and dissensions which, down the ages have admittedly divided East and West in the political and economic field cultural exchanges have always been maintained I do not wish to go right back to ancient times and speak of the intellectual contacts between the ancient Egyptians and the Persians, the Greeks and the Romans nor shall I refer to the age old role played by the Mediterranean in serving as a bridge between the cultures of East and West But I would point out one thing—that Christianity however Western it may appear, was in fact born in the East

I should like to dwell for a while nevertheless, on Moslem civilization It is a great mistake to think of this civilization as the product of the Arab peninsula alone On the contrary the Moslem world was subjected to a wide variety of influences Manichaeism, Mazdeism and Sabeism were all expounded and discussed in Moslem countries Persia bequeathed to the Arabs many of her political and administrative institutions,

nor must we forget the influence of India, which is very evident in Moslem culture and traditions

For their part, the Arab borrowed likewise from Greek civilization They were acquainted with most of the works of the great philosophers and scholars of ancient Greece, from Plato to Plotinus, Hippocrates to Galen, and Euclid to Archimides, which they translated into their own language though Renan was doubtless exaggerating when he remarked some 100 years ago that all the Arabs did was to adopt the whole of the Greek encyclopaedia The fact is that Moslem civilization is a meeting ground for the ideas of both East and West

On the other hand, Moslem civilization, in the Middle Ages exercised a great influence on the Western world From the twelfth century onwards, we find Europeans translating into Latin, directly or indirectly Arab works on theology, philosophy, medicine, mathematics and astronomy These transla tions played an important part in Christian scholasticism, prepared the ground for the Renaissance and contributed to the development of modern philo ophy and science

A few examples will suffice to illustrate this point

Saint Thomas, as is known criticized certain Arab doctrines as though they were those of his contemporaries, so much so that people even spoke of Latin Avicennism and Latin Aver rhoism and Arab medicine particularly the theories of Razi and Avicenna was taught in the schools of Venice and Padua up to the sixteenth century Ibn Sina expounded the theory of the earth being round long before Copernicus and Galileo and refuted the science of alchemy and the doctrine of the transmutation of metals long before Lavoisier These and other Arab ideas filtered through to the West And finally, certain rules relating to observation and experimentation rules on which modern science is based came to the Latin from the Arab world

It is thus clear that though, geographically and politically speaking there was a sharp distinction between East and West, this in no wise prevented the exchange of intellectual ideas in ancient and medieval times between human beings of whatever creed or country

The Modern Age has witnessed the continuation of these exchanges which have developed still further owing to the

tightening of the links between East and West Need I point out that every person round this table has, in his make up, something that partakes of both East and West? The time has, I think come particularly in view of what aviation and the radio have achieved, when we can indeed speak of one world

Another distinction must however be made—the distinction between what might be called national and international values In every age, each nation or community has had its own set of dogmas laws and traditions—in other words its own code of moral and material values Even today, chauvinistic nationalism sometimes pushes national characteristics and peculiarities to extremes but even so it may be said that national values are coming more and more to be coloured by the common heritage of human civilization as a whole—by what I would call international values

It is these latter values that must be stressed They are the creation of no single people nor of a single country Who, for instance, would maintain that freedom or tolerance were ideas invented by any one nation? On the contrary, they are the outcome of a world wide process that has continued in time and space throughout the ages And it is our duty to further and develop this process for it is in it that our true wealth and strength lie

These international values must be taught to every citizen of the world and imprinted on his mind They must be the basis of any ideal education It is not enough to know them, they must be firmly believed and religiously respected It is for the leaders and the great thinkers to shoulder the heavy task that this involves

Today these international or rightly speaking human values are not always accorded the respect they deserve They sometimes remain a dead letter and are often treated not as ends, but as means Many conflicts and much human suffer ing would be avoided if they were professed sincerely If we wish ever to attain world peace and tranquillity, they must reign side by side with national dogmas in the minds of the younger and coming generations

Before such values can be genuinely accepted however, they must be defined in full and generally agreed upon This is admittedly no easy task, but Unesco which speaks for man, will, if it succeeds in this, have a fine achievement to its credit

The Buddhist Point of View

by

G P MALALASEKERA

WE stand at one of the great turning points of human history oppressed with problems irresolute and un certain of our way None of the riddles which face us de manding answers is more urgent than that of preventing the ruinous recurrence of war The fate of the world trembles in the balance Mankind has yet to decide whether there will be a future war, more disastrous than anything we have had so far, or whether war will be ostracized for ever There seems to be no other solution

All around us are conflicting national interests, racial pre judices rapacious greed, class and group animosities con flicting creeds and ideologies struggling in a mad scramble for priority and advantage A sense of futility, even despair seems to overshadow man s endeavours in the search for happi ness and peace We seem to have plunged from the nightmare of war into the even worse nightmare of peace Meanwhile, our destiny is being determined by so called statesmen trained more in manipulation and cold sagacity than in in sight and imagination They pay lip service to justice and democracy, while manoeuvring for positions of advantage and superiority for themselves and those whom they seemingly represent Behind their smooth façade of words there goes on all the time bitter haggling accentuated by bland inter national blackmail and power threats euphemistically called diplomacy The simple common cause of humanity is for gotten Almost forgotten also seems the grisly reality of war, with its senseless slaughter savagery and the imponderable losses of economic destruction

Such is the basic problem that has to be recognized Is the world to have war—cold war is as bad if not perhaps worse than hot war—or shall mankind enjoy peace, which is the

common need of distraught humanity? For without peace there can never be happiness, and happiness is the goal of all human endeavour But what do we mean by happiness? Looking down the ages and at what is happening around us it is clear that men s ideas of happiness differ, they evidently depend upon the kind of philosophy, the sense of values, which influence them Not that all men are philosophers, but we all have our attitudes to life and that broadly speaking, is philosophy

It is his philosophy that gives to man a feeling of stability and of confidence It furnishes him with a purpose for his life To be really useful it must also furnish him with a way of life, not merely theories about life The way must mean more than just mere living an occupation a profession, or a job These are just modes of life not life itself The way of life must be such that it can actually be lived, experimented with, experienced *A practical philosophy must in addition, provide the* man who accepts it with convincing reasons as to why he should follow a particular way of life in preference to others Besides these conditions it must either actually give him the answers to the questions which inevitably arise in his mind about life and the world around him, or at least, point out the means whereby the answers can be discovered

In the case of most men, their religion purports to provide them with such a philosophy True religion like true philosophy is a practical thing It recognizes for instance that such affairs as the building of roads and houses growing food and changing external circumstances, are not the only practical things, that it is equally practical to change one s own inner behaviour, to discipline oneself in family life and social relations to steer one s desires from material to spiritual goods to develop the mind so that it can become a far more potent force than the body

Religion is thus a way of life, but life cannot be lived without reference to the facts of life, and the facts of the world in which we live and have our being, the world of physical and mental things A doing, a behaving an attitude, must be in relation to a given state of affairs here and now, and where an ideal is contemplated, such ideal must be capable of being translated into a plain fact Man should be and is, one of the facts of the most primary importance in any religion or philosophy,

and in as much as religions and philosophies differ from one another, it is inevitable that they should differ in their concept of man as well

Now, the ideal concept is one which is shared alike by all who are concerned It must possess a syntactic community of meaning whereby people using it can employ it in regard to problems that concern all of them and reach results which are coercive to each Is it possible to discover such community of meaning in the different philosophies of the East and the West regarding the concept of man?

It must be remembered at the outset that in their attempts to arrive at ultimate truth, East and West generally speaking, do not adopt the same methods The West relies mainly on the deductive and inductive methods of logical reasoning the principles of non contradiction and empirical verifiability The East on the other hand gives the crucial role not to logical method but to a supra rational intuition, consisting of subjectively variable mental processes not recognized or trusted by the West Both it is true employ the analytical method, but in widely varying degrees and not necessarily for the same purposes There is thus a big gulf between the two kinds of system, which at first sight seems almost unbridgeable with regard to fundamental facts But much can be achieved to bring them together Here as elsewhere free and equali tarian co-operation will succeed in establishing a harmonizing synthesis which however in the nature of things will be an orchestral rather than a single instrument harmony

What can Buddhism contribute to such a synthesis? What is the concept of man as found in the Buddha s teaching?

It is inextricably bound up with the Buddhist concept of the world Buddhism studies nature the principles governing the make up and course of specific concrete facts It has its own cosmology and philosophy of nature although these are not its main concern It is concerned with this world as a given fact with its manifold of things and relations But it does not stop there It wants to get a picture of reality if only in order to see the ultimates beyond or deep within the world It does not seek knowledge for its own sake but for the attainment of the Good The Good is not to be found in particular events of nature s course in the moment to-moment happenings of life Nor is it to be found by reorganizing the world with all its

complexity, in remoulding human society or in reforming the State The Good is to be attained by the realization of ultimate truth, by the understanding of things as they are

When such understanding comes says the Buddha, we shall see the world as a scene of misery, not because the things of the world are intrinsically bad, but because of our wrong attitudes towards them The cause of misery is attachment, craving Pleasure is not in itself sorrow but it leads to sorrow because it is fleeting We want the pleasure to last, but it will not obey our behest Recognition of this fact is not pessimism, it is wisdom It is because we expect and desire a permanence which is not possible that we are sad when our expectation is not fulfilled The teaching of the Buddha that there is nothing permanent in the physical or the psychical, no lasting substance or perduring ego is a statement of fact and not a lamentation

So also is the Buddhist teaching as regards time There is *nothing called time, in the sense of anything static Time is but* a process a continuous process of coming to be and passing away The Buddha does not say as some would have us believe that everything perishes as soon as it is born What he does say is that there is neither birth nor death but only a *becoming* a *coming to-be a process of change It is not just destruction* or death but also a constant renewal a new upsurge of life all the time To try to perpetuate the world would be merely folly because there is nothing eternal except the present, the now which is always now

The fact that everything is in a state of change should fill us not with despair but with joy it is precisely because everything changes that there is even the *possibility* of perfection and betterment If there were no change how could the bad ever become anything good and the imperfect become perfect? Progress improvement and increase are possible only because of this fact of change Change means not only destruction but also continuous construction Becoming is synonymous with growth but growth can be either into a better or into a worse The perfect, in Buddhism is not what is everlasting but what is beyond time a temporal It is not by trying to make the fleeting pleasure or joy permanent that one can get happiness It *cannot* be made permanent because apart from the fact that a pleasure must inevitably pall if it lasts for ever, it is not in

the nature of things to have permanence When however, we realize that change is inevitable, and understand the cause for it, we cease to regret the transience of things and are un affected thereby Sorrow consists not in the impermanence of things but in our attitude towards that fact To say that progress requires a perduring entity is a fallacy Identity yes, but not perdurance There can be identity without permanence This is what the Buddha means when he says that a man is neither the same nor another from day to day, from moment to moment There can be continuity of identity without a per manent entity as substratum thereto

We cannot realize the truth about the world if all the time we are completely immersed in it Hence the need for turning away from the world, the cultivation of detachment in order to get a right perspective This is not the same as running away from it, an attempt to escape but merely a withdrawal temporarily till the truth about the world is understood The saints and the mystics, the ascetics and the *Bhikkhus* are those who have voluntarily renounced the world in order to get a clearer vision which they then invite others to share with them Such detachment is necessary in order to secure equanimity which is one of the requisites of happiness Happiness is not in external things but within ourselves It is a state of mind the fruit of complete understanding Equanimity is not possible however, especially to sensitive natures if all around one are suffering and misery No man can be happy by himself for himself Hence the Buddhist ideal of the *Bodhisattva* the being who ultimately becomes a Buddha who will not cross the threshold of Nirvana till he can bring also others thereto

The world is full of misery the wise man will recognize this fact and he will do all he can to alleviate this misery himself and persuade others to do so too The misery is partly physical and due to ignorance and wrong kinds of behaviour behaviour influenced by motives of greed and ill will the delusion that selfishness pays dividends and that money and power can secure happiness There is sickness in the world and discom fort, destitution oppression hatred and prejudice These can and must be minimized in every possible way The Buddha declares that good health is among the greatest of the good things and that there must also be sufficient food To attempt the good life on an empty stomach would be mere folly The

needs of men regarding food and clothing shelter and relaxa tion are, according to the Buddha, primary and essential needs and must be satisfied Man has to live before he can live spiritually his physical body is the seat of all his endeavours, including those that relate to morality and the higher life It must therefore be tended and looked after Buddhism does not insist on the suppression of those desires and emotions which well up from the human heart, except by those who feel a special call for their sublimation To the others marriage and the founding of a family are considered helpful in that they make the individual less egocentric and selfish But domestic happiness is not regarded as the goal of human life It is only a stage in spirituality

In the satisfaction of one s desires, as in all else the middle way is considered the best that which avoids extremes Un thinking and unnecessary gratification of the body creates newer and ever greater appetites and consequent dissatisfac tion Life becomes a state of slavery as soon as we make of it a search for comfort as soon as simple physical needs are de veloped so as to grow into physiological greed Never are desires satisfied by indulgence, they flare up like the fire to which fuel is added

A man is a member of a community of beings and without the community he cannot live This community is not of living beings alone the whole world is his kin animate and inanimate alike The bifurcation in nature between living and non living is only apparent, what we have in the world are merely ordered systems of many magnitudes, expressions of the life field Buddhism recognized this fact many centuries ago and anticipated the discoveries of modern science But it is with other human beings that man is primarily concerned and his immediate relationships are with them Whatever the *community does affects him and conversely, whatever he does* affects the community An individual is like a wave in the ocean ocean and wave mutually affect each other

This conception of the individual and the community as being interdependent also means that there are mutual obliga *tions The community must look after the individual and* provide him with a sense of security On the other hand the individual has certain duties to the community to which he owes his very existence The most elementary of these duties

are expressed in what in Buddhism are known as the Five Precepts which form the basis of man s morality A man must hold life sacred and not harm in any way the progress of any living being He must have regard for the sanctity of what legitimately belongs to others and thus not only refrain from deliberate theft but also from exploitation of every kind He must exercise restraint in his desires and not be greedy in gratifying them He must be honest and truthful in speech, avoiding harsh words and slander, malicious or false propa ganda and speech that creates discord He must refrain from all things that rob him of his power of reason, his powers of judgment and his balance of mind

These obligations he must honour in the interest both of himself and of others On the positive side he must assist all enterprises that increase the happiness and well being of humanity, by his thoughts words and deeds Above all he must seek enlightenment by broadening and deepening his mind by the pursuit of truth and beauty and goodness The practice of goodness and the appreciation of beauty are not ends in themselves Goodness is necessary because there can be no happiness without it it is absolutely essential for that peace of mind without which there is no real happiness The saying that there is no peace for the wicked is quite literally true

The individual is in debt to the community for supplying his needs and he should seek to discharge his debt by service to the community All men are his brothers not because they are the sons of the same heavenly Father but because they are all of the same flesh and blood as himself—the Buddhist con ception of the brotherhood of man has a wider embrace than that of theistic religions In order that he may be of service to others the individual must make himself efficient in every possible way developing all his skills all his powers of body and mind and intellect his feelings and emotions and the aes thetic side of his being Goodness is that which promotes hap-piness The definition of goodness in Buddhism is also that which develops "efficiency in oneself and in others All evil hinders such efficiency It is not the nature of the contribution a man makes to the progress of the community the kind of work he does, that matters chiefly but the spirit in which he makes that contribution It should be informed with love and devotion selflessness and wisdom

The world and everything and everyone in it are governed by certain laws, says the Buddha which are inexorable As long as men live in harmony with these laws, they will be happy In fact, the word used in Buddhist texts for un happiness (*dukkha*) has among its many meanings, that of ' dis harmony When man attempts to dominate nature, or as is commonly expressed, to wrest from nature her secrets if he thereby upsets the workings of these laws he does so at his peril, unless he can restore the balance in some way Among the laws that govern the world and man, the most important, according to Buddhism is that known as the law of *Karma* Briefly stated it means that everything that is is the effect of a cause and is itself the cause of another effect *Karma* means deed and the result of deed The law applies to the realm of morality, the principle of cause and regulated course of things There is thus nothing capricious or chaotic As we sow, so we reap What we are and what circumstances we find ourselves in are dependent on what we were and what we did Similarly what we shall be will depend on what we do now Nothing is lost which has been earned by work and nothing comes which is not deserved Every action has a double effect, it brings its appropriate reward and also affects character The reward may be reaped either here or in a hereafter either in this life or in a later one Nothing and nobody is exempt from the law of *Karma*, not even the God mentioned in theistic religions It is inexorable and unfailing

It is necessary to state that the Buddhist doctrine of *Karma* has nothing in common with fatalism or predestination for in the Buddhist teaching *Karma* is a *continuous operation* The present is the result of the past but the future will depend entirely on the present Over past *Karma* we have no control but the future is absolutely ours, because the issue depends on ourselves *Karma* is self-operative no god or devil can interfere with it except the deed itself Events are impelled by pre ceding conditions, causes that man could by intelligence and good will study and govern suspend or intensify If everything is the effect of a cause or causes, the happiness and misery of the world must also be the result of causes Change the causes and we can change the effects thereof Thus the freedom of man is proclaimed in the highest possible degree He is not merely a partner with God in the work of creation but the

creator himself War and peace poverty and wealth, are ours to decide we ourselves are solely responsible Progress is not inevitable but it is completely possible We can begin the control deliberately, now for every moment provides our opportunity We do not have to wait upon anyone else Far from denying the values gained in momentary existence Buddhism finds value in the developmental changes in existence In order to fashion the future the past does not need to be destroyed, indeed, it cannot be destroyed But we can build upon it change it, improve upon it There is nothing to prevent *it from being an incremental change not hopeless but* positively hopeful Life has every opportunity to make of itself an outgoing spiral, positive, coercive and good

To achieve this, purposeful thinking is necessary thinking over all possible ways reviewing the causes of unhappiness and formulating the details of the upward path Reason and logic should not be given the exclusive right of decision though they should not be excluded Science has its uses for a fuller and wider life but science alone by itself cannot make mankind perfect Inasmuch as according to the Buddha, ignorance is the root cause of unhappiness happiness is to be sought through knowledge and wisdom, and insight Knowledge is to be acquired in every possible way through study through discussion and through contemplation contemplation being the best Such contemplation is not glassy eyed gazing into vacant space but purposeful activity of mind where knowledge and understanding are co-ordinated The way thereto is reflection directed to the discovery of ultimate truth That is the best kind of reflection but all kinds of reflection are to be encouraged They provide at least much needed breathing space from physical activity Now more than ever before, is such periodical reflection necessary to those who live in this age of speed, when much else besides time hurtles along It is often useful to slow down the tempo of living even to practise occasional inaction

Knowledge gives power but it is understanding that directs the wise use of that power Through knowledge men can delve into the very depths of cosmic power, as they have done already but unless god like power is coupled with god like understanding and insight the power that men have obtained will recoil upon themselves to their destruction What is

important is not to discover how men can destroy each other but how they can live together for the common good Under standing is reached by experiment and investigation, by prac tical living and by constant awareness Great emphasis is laid by the Buddha on awareness or alertness of mind It is an essential concomitant of understanding

The path of self development, though often spoken of as a road is not a progress in space and time It is rather an ingress into our own nature so as to comprehend it wholly Learning, science art and philosophy all give us some kind of insight into truth but they are only aspects of truth All these aspects must blend into a single harmony This is possible, according to Buddhism only through right understanding Understand ing is not just knowledge, for knowledge is of facts whereas understanding is of causes and therefore, ultimate It is the lack of this harmony which is responsible for the disintegration that characterizes modern life, whether we think of ourselves as individuals citizens of a country or members of the world wide family of mankind The causes of this disintegration are the chasms of prejudice, ignorance and fear which divide mankind into fragments The world has already shrunk into such small proportions that no significant event can take place anywhere without the effect being felt everywhere But men have failed to realize the import of this and persist as though individuals and nations can find happiness through means that only promote selfishness A wave is not just a part of the ocean, it is the very movement of the ocean and cannot be separated from it When men realize this, conflicts will cease

One of the ways of developing such a world consciousness is the search for the basic concepts and the underlying prin ciples from which men of various races and creeds draw their inspiration in the pursuit of the higher life These concepts almost invariably deal with the structure of the universe, the nature of life and the goal of human endeavour They serve as the common roots from which the various branches of the human family draw their vitality Such a search is most likely to end in a sharing of our beliefs and shared beliefs have a great validity in promoting friendship Mere morality is not enough, nor should morality be restricted to the cultivation of the sterner virtues The gentler qualities should also be practised civilized conduct and generous behaviour, the

spirit of tolerance, of live and let live of trying to understand the other man s point of view of diffidence, which leads to humility These are often overlooked and are in need of constant reinforcement

The Buddhist doctrine of *Karma* has as its corollary the doctrine of rebirth Man thus inherits the results of his actions in past lives He is also, in addition, heir to the past of the human race Thus according to Buddhism, men are not born *equal but the inequalities are individual and have no necessary* relation with race or caste creed or place of birth or colour of skin Every man has value and is due both to give and to receive justice mercy and kindness No individual or group has any right to dominate or exploit other human beings or groups and differences of race and the like afford no justifica tion for such domination There is no justification, either for dividing human beings into Orientals and Occidentals and to maintain that there are perceptible differences between them in physical ability intellectual capacity, virtue or creative action They react to similar emotional influences are subject to the same diseases and show the same signs of restlessness suspicions and psychoses In other words, they show a common humanity Racial segregation and discrimination are evil There is no such thing as original sin in Buddhism on the contrary, man's nature is declared as having been originally pure and later become polluted by evil association

The potentialities of man are unlimited It is a man that becomes a Buddha an Einstein a Mahatma Gandhi Men must therefore be given every opportunity to develop their personalities to the fullest possible extent for their gain is the gain of all mankind No man is beyond redemption no man should be shunned or treated as if he were beyond the pale of human fellowship The light burns within everyone however dimly, and can be fanned into flame The Buddhist books con tain the story of the brigand Angulimala who had committed 99 murders when he met the Buddha The Buddha preached to him the way of the Good Life and Angulimala became an *Arahant* a Perfect One Perfection is not already present within us, but the seeds are there and will grow and blossom if the requisite effort is put forth and the conditions are favourable It is false to say that human nature will not change although it may not necessarily change overnight

In Buddhism there is no place for a Saviour men must solve their own problems without waiting on the agency of some external power If they do not make up their minds to be good and wise they will not be able to escape the results of their ignorance and their evil actions There are two aspects of life the material and the spiritual Happiness comes only when these two are synthesized Buddhism does not despise material welfare but it demands that the things of the flesh must not receive undue attention and that they should be brought under the subjection of the spiritual It insists on personal discipline and the simplification of personal life so as to reconcile one s demands with the needs of all mankind In the human family no responsible member will consume more than his share and this too must be reduced to a minimum The good man, in Buddhism, is the one who is *subhara* easy to support without being a burden on the community

There is no intrinsic value in poverty Wealth is not a curse if it is kept under proper control and given no more than its due place in the scheme of things Wealth has its value, which consists in the use made of it If a man thinks he can buy his pleasures and reliefs indefinitely he is bound to be disillusioned Such desire only creates an endless multiplication of appetites and wants, resulting in his unhappiness because physical appetites are never completely satisfied The Buddha, far from discouraging the acquisition of wealth gives suggestions—the Buddha never lays down laws—about the proper disposal of one s income It should be divided into four portions, he says one should be used for personal needs, two should be invested and the fourth laid by for a rainy day He does not say what amount should be spent in good deeds, for that would depend on the degree of one s spiritual development Earning is not for hoarding but for spending in the service of oneself and of others Generosity is extolled as one of the basic virtues The Buddhist view of property is that it should be held as a trust

Wealth must never be earned by unrighteous means by exploiting the misery of others their greed or their folly Money obtained by such methods as the sale of liquor and drugs of animals for slaughter or captivity, by following professions which involve loss of life or limb or the rights of others or by the manufacture and sale of armaments, is expressly condemned The Buddha is perfectly certain that vio-

lence can never be overcome by violence Hatred never ceases by hatred but by love forms part of the bedrock of his teaching Violence in any shape or form on any pretext or excuse whatsoever, is unjustifiable There can be no such thing as a righteous war Anyone who believes in the efficacy of violence heps to perpetuate conflict and to make war inevitable The total abolition of war is undoubtedly a very difficult problem but Buddhists believe that it is not incapable of solution What is needed is a spiritual revolution, a change in the human heart and such changes can be brought about if men have sufficient faith in themselves The example of the great emperor Asoka who, having once been a ruthless warrior later became the gentlest of men, is a case in point The eradication of war is a moral responsibility devolving upon every single human being Mankind will not renounce violence as a whole until we have renounced it within ourselves as individuals We cannot shift the responsibility upon others It is we who as individuals contribute to the mass hate of the world The militarists exist only by the sanction of the people, who are their principals War will never bring happiness Total disarmament must come if such be the genuine and determined wish of the majority of mankind It must come through a world wide spiritual renaissance The generality of men and women now abhor war more than ever before because, with progress , wars have become more horrible and disastrous War no longer possesses the glamour of chivalry It is now conducted as a grubby and laborious business by proletarian robots most of whom are not in the fighting forces at all We must of necessity ostracize war or make up our minds to perish entirely

But like everything else war has its causes These must be eradicated if war is to disappear As the Buddha declares in the *Kuaddha Sutta* of the *Digha Nikaya* men are virtually certain to rebel violently against gross oppression and intolerable suffering No peace is possible as long as conditions of obvious social and material inequality exist We cannot cure troubles whose real roots are to be found not in some ostensible criminality in men but in the unresolved problems of daily existence, by the mere introduction of fine principles of law or by uttering platitudes As long as men and nations are governed by the desire of making money and "getting on , we must

expect social inequality, greed, imperialist domination, dehumanization of life and consequently, war Men must learn to escape from the brutal utilitarianism of material things The only solution is the cultivation of spirituality The Buddha declares emphatically that there can be no substitute for *dhamma* or righteousness

The name given by the Buddha for religion is also *dhamma* because to him religion is synonymous with righteousness Religion is, above all the understanding of spiritual values It is not the name that is given to religion which is important but the search for the supreme good That is why throughout history all the vital changes in civilization which have spelt human happiness have been linked with religious beliefs and ideals If the chaos of present day civilization is to be remedied, there must once more be a resuscitation of spiritual values in place of the materialist values of the stock exchange and the market place which now dominate the human scene

But, if religion is to be really effective in promoting our happiness it must inform every aspect of our lives, the social and the economic the political as well as the domestic It must not be confined to the church and the temple to Sundays and Sabbath days It must envelop our being like the air we breathe There cannot be one code of righteousness for individuals and another for the mass One of the greater tragedies of the modern machine age has been the emergence of the anonymous mass man, with no cultural idealism disinclined to follow any other course than that dictated by his own obstinate self interest The establishment of universal media like the radio the cinema and national newspapers, by which the mass can be influenced and controlled, has greatly aided this calamity Religion if it is true religion must find some kind of meaning for mankind and the cosmic process as a whole compatible with and related to its meaning for the private individual

It is the responsibility of human beings to find the solution The good way of life must be followed regardless of expediency This is possible only if there is a metaphysical basis for moral obligation Morality which does not spring from a cosmic motive from the conception of a fuller life, can have no solid foundation A man must first have self knowledge, i e a conception of himself That will depend on his conception of

ʻ y, the nature of the world in which he lives and the ies that govern life Good conduct is called in Buddhism *ammata*—the acceptance of and acting in accordance with ity, things as they are, *yathabhuta*

Education that will fit man for the good life must provide a convincing metaphysical basis The attainment of happiness is the goal of mankind But what is happiness? The Buddhist word for supreme happiness is *Nibbana* (Nir *vana) It is difficult to* describe *it in* positive terms because one of our concepts quite fit in It is without attributes, but not 'characterless All that can be said about it perhaps is it is complete emancipation It cannot be attained except , one who is trained to look upon others as upon himself, to fy himself with the whole world This supreme happiness ist be attained in this world and not after death That should least be the aim

In the Buddhist way of life freedom is of *the essence of* appiness It is not merely political freedom economic urity and the guarantee of social rights that are required, but freedom which is felt as a living power within and around ieself Men cannot be free merely because they are told they free Freedom is very largely a matter of attitude to things ur relations with them The ideally free man is in Buddhism ae *Bhikkhu* (or monk) who spends his days in contemplation ondering over the mysteries of life wandering far and wide the spiritual sentinel of the human race His very striving or perfection and his experience of it when he attains it are great blessing *to* the whole race He has no private ambitions r desires Pleasure and pain poverty and wealth success and ailure make no difference to him When he has achieved the ie goal he has no need for the things of the world He eckons all to share in the *indefinite happiness which* has come his though few will follow him

That is the ideal freedom but meanwhile the sense of rela onship that will result in freedom can best be established in he field of education Education must fundamentally be a aining in the art of living the art of putting all things in right order, so that our every function interest and activity may find its appropriate place It will make due ion of the great differentiations existing in the world ie natural levels of higher and lower degrees of development

and achievement It will ultimately succeed in evolving a universal culture a culture which will make allowance for the fact that 'men are ever pursuing the same truth on different landings It will not, however be a mercantile culture , watered down to suit everybody It will be a culture of unity, rather than of identification of integration rather than of cohesion It will take account of the qualitative achievements of man in the past and preserve all that is valuable in them But it must have its vision in the future

The sight that greets us when we peer down into the Gehenna of the warmongers is terrifying But let us not lose courage In many parts of the globe there are men and movements seeking the happiness and peace of the world, attempting to integrate the clash of bias and interest Perhaps, nay probably, religion will provide the surest basis for such integration, for the word itself means b nding together A new age is in the making and we are witnessing its birth pangs A united world is no longer a dream belonging to an irreducible, infinite future, but a vision almost within grasp

Somewhere beyond the railheads
Of reason South or North
Lies a magnetic mountain
Riveting sky to earth

Let us seek it

Towards a New Humanism

by

André Roussfaux

THE major problem of today is probably that of bringing the East and the West into harmony This recent statement by Mr René Grousset seems all too topical to judge by certain events in the history which is being written before our eyes

But the more troubling this disharmony the clearer it becomes that we shall only overcome it by a reconciliation which rises above it And if we go to the bottom of all the misunderstandings by which the East and the West seem to be divided we shall have to ask ourselves whether they do not proceed from a maladjustment of our respective moral responsibilities Thus we shall see that the problem of the relationships of East and West possesses this remarkable aspect that the political and economic factors are not only bound up with the spiritual but are dominated by them There is perhaps no question racking the world today in which the primacy of the spiritual is clearer or more imperious None of our great human problems is more essentially a spiritual and moral problem both in its data and in the solutions it calls for Thus when intellectuals take a hand in it they can feel that they are in an element where their activity, far from being an intellectual luxury may be extremely effective

Let us first define the relative importance of spiritual causes in the difficulties through which the relations between East and West are now passing

In the last century these relations were based on the domination of Eastern life by Western activity The point to emphasize here is not so much the mere historical fact of this domination as the spirit in which it was imposed by one side and to some extent accepted by the other

The West posed as the representative and the master of a

civilization which it brought with it, which it taught, which it bestowed if need be, with condescending generosity, on passive recipients It was moreover convinced that it was offering to these backward civilizations its own progress an intellectual progress directed towards scientific development and a progress in the sciences directed towards their practical application When it built railways or electricity stations it thought that by so doing it was winning, for itself and for its subjects a higher level of civilization And it is doubtless true that indisputable physical progress, from which every human being could physically benefit, was made in such fields as that of material comfort, of hygiene and of certain living facilities But these benefits stamped as they were with the materialist outlook, did not go beyond the category of techniques They brought no spiritual message with them On the contrary, they turned the minds which concentrated on them towards a specialized form of intellectual activity, cut off from that general human culture which the West *has long called hu manism*

There was thus a fundamental error in mistaking for progress and for the uplifting of man what was at bottom a blow at his unity and at his real greatness The West was to become aware one day that this error was at the root of its own mis fortunes it was also to poison its relationship with the East, and through this relationship the evolution of Eastern life itself

In all the Eastern countries where the West extended its conquests its technical superiority began as the instrument of its domination It was this superiority that secured the triumph of its arms of its equipment of its institutions of every kind But above all it was this that placed it, in relation to the dominated lands in a position of superiority whose principle was at bottom, admitted For the East tolerated with ill grace and ended by not tolerating at all, the military con quests the foreign laws and the enforced governments that the West brought with it But it did not resist—with few exceptions—the locomotive, the dynamo and the telephone The West, which was not able to win acceptance of itself as a conqueror, was at least able to win acceptance of the instru *ments of its conquest and to obtain for them as much respect* as it gave them itself So that finally, at the close of the tale

when the conquerors had been sent packing and the conquered had been freed, human liberty and dignity had to outward appearance won all along the line but in fact there was nothing left but slavery For the West the slave and accomplice of a soulless intellectualism had succeeded in betraying the East into an analogous slavery to the modern idols worship of which has subjugated the world

And this is not all The East, which imagined itself to be gaining through this development is in danger of losing in it a spiritual treasure which was its very own When its peoples bowed to the Western conquest they were for the most part in a somewhat dormant phase of their civilization It might well be asked, indeed to what extent their spiritual life was not really passing through a period of lethargy (Here there is obviously room for distinctions between spiritual positions that must have varied with religions and peoples) On the other hand it is possible that the outward show of a purely ritual fidelity to somnolent religious customs was strengthened by the conviction which the West brought in with its intellectual imports that the progress of civilization led in the opposite direction from these customs and rites At a certain period, the West included the temple and the mosque in its shop window of picturesque properties decking them out with the heart breaking magic of objects in their death throes this was not simply because of a positive taste for certain purely aesthetic aspects and a certain silent poetry but because these dead or dying beauties were all it had preserved of things that its intelligence had emptied of their content

The awakening of the East has come Has it taken the form of a return to its own spiritual sources? That has occasionally happened and in an impressive fashion But it has to be admitted that generally speaking the East embarked on its renaissance with the idea that progress for men and for peoples lies in the direction which Western intellectualism taught it The political freedom it has won does not prevent it from maintaining its dependence on resources which it continues to ask from the West These resources take the form of what the West has in greatest abundance and what it produces best for itself —techniques The West has allowed the spirit and the principles of its own civilization to become obliterated in the sovereignty of techniques its successes are machines and mechanical

skills, it is these successes which it holds up as an example and which it is capable of teaching And the East which prides itself on having made up its lost time (lost by reference to this conception of progress) believes that these successes are really what makes a nation civilized

But once the sovereignty of techniques has been established in the material field there is too little either of highminded ness or of disinterestedness there for the propagation of techni cal civilization not to turn the tables on the tyros who had believed in it too wholeheartedly Dissensions of a materialist kind are then seen to be at precisely the opposite pole from the spiritual union for which we are seeking An Iranian writer, Mr Rashid Yassemi has given a convincing demonstration of how Eastern peoples go astray—if fascinated by Euro pean technique , they become the victims of an inferiority complex which dooms them to imitation [1] This is the vicious circle in which the East allows itself to be imprisoned once it has yielded to the mirage of technical civilization

The West is guilty twice or thrice over of this calamity For, first it made technical supremacy a criterion of civilization for itself then it passed on this false lesson to others and finally it claimed that its own superiority in this field was un approachable—not to speak of the interested motives which were at the bottom of this reasoning As for the East it has every right to wonder why the West should deny it the oppor tunity of doing what it puts forward itself as most worth doing But in so far as the East itself succeeds in this direction it will catch up with the West in the state into which the latter has got itself today the state of a civilization in danger of death

More than one modern thinker has perceived this evil which has been disseminated throughout the world by the contagion of an error We may quote in this connexion the following remarks made by Lord Portsmouth in his book *Alternative to Death* [2]

"We have committed a crime against the Oriental countries by the arrogant super imposition of doubtful alien techniques and ideologies Spiritually we have been iconoclastic and for that far more than the fact that we have appeared as conquerors, we shall not lightly be forgiven

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[1] *L Âme de l'I* Paris 951

[2] Lord Portsmouth *Alternative to De th* (944)

Must we then look for a complete reversal of this state of affairs, that is to say a resurrection of spiritual life which would demand the abject capitulation of technical civilization? The question is not so simple as that for here we are concerned not with abstract values but with a human problem It seems to me to have been admirably stated by Dr Thérèse Brosse in the following lines

The most urgent problem of our times is the foundation of a science of man which shall not be only a science of the *human animal* but a science of the *complete man* with all his spiritual values studied both from the individual and from the social point of view Man has just wrested from matter the secret of its universal forces Unless he simultaneously turns the same zeal for discovery on himself in order to mobilize in his consciousness all his potentialities of understanding and of love—or if this power over matter only falls into his hands to sow terror and death—then it is the end of humanity

The problem is therefore a universal one not a mere question of settling an opposition or finding an equilibrium between East and West considered as two antagonistic worlds It is indeed for both of them united in the same danger and face to face with the same destiny the same problem of the reconquest of a real and complete humanism If they are to succeed East and West must take the same road in the direction opposite from their common error

Let us start with the East which should be the less committed to the error since it was attacked more recently and by contagion It must in any case cease to revere as unquestionable principles of civilization certain formidable elements that go to make up political and social power in our times It would be hard to find a more pertinent comment on this than the warning given to one of the great civilizations of Asia that of India by Aurobindo in his message to the University of Andhra on 11 December 1948

"There are deeper issues for India herself since by following certain tempting directions she may conceivably become a nation like many others evolving an opulent industry and commerce a powerful organization of social and political life an immense military strength practising power politics with a high degree of success guarding and extending zealously her gains and her interests dominating even a large part of

the world, but in this apparently magnificent progression forfeiting its *Swadharma*, losing her soul Then ancient India and her spirit might disappear altogether and we would only have one more nation like the others and that would be a real gain neither to the world nor to us There is a question whether she may prosper more harmlessly in the outward life yet lose altogether her richly massed and firmly held spiritual experience and knowledge It would be a tragic irony of fate if India were to throw away her spiritual heritage at the very moment when in the rest of the world there is more and more a turning towards her for spiritual help and a saving Light "

A warning like this holds good for other peoples and other civilizations of the East And the last words of the quotation show the healthy current which is stirring nowadays, from India first of all but also from the whole East, towards Western minds—not merely the tide of erudition on which the science of the Orientalists has so long lived, but a current of active philosophy propitious to a fruitful intercourse leading to common spiritual progress

If I talk here of intercourse it is because the time has come to point out that the West has more to contribute to this spiritual revolution that beckons to us than mere penitence for its errors and submission to an Eastern spiritual supremacy which it had failed to appreciate Once more let us set aside any antagonism and seek for points of convergence The error the West committed struck first of all at itself That error was committed at the expense of resources which it possessed which it has neglected not to say compromised but which could none the less be brought back to honour Since the West bears the prime responsibility for the ills of the modern world, the question how it can rediscover itself is one of the most important we have to examine

Let us first make it clear that what has been argued above gives us no warrant for summarily setting up a West that is all materialism against an East that is all spiritual We have been obliged to simplify things a little We should come closer to the truth by saying that the Western spirit which imposed itself on the East was that of the nineteenth century and was that aspect of it furthest removed from the very significant spiritual renaissance which the West and France in particular, has experienced in the twentieth

Today, then the dramatic conflict between the materialism that leads to death and the spirituality that saves is being played out, in accents of tragedy in the very heart of the West There is more than one important work in the most modern French literature to bear witness to the fact Bernanos *La France contre les robots*, for instance or Simone Weil s *Enracinement*

When the Western mind attacks this problem moreover, it does not throw itself headlong into the naive solution which consists in disowning the conquests of science and declaring them incompatible with the life of the soul It calls the attention of thinkers to the observation, never made before that these intellectual conquests were achieved in contempt of the life of the soul, with which the conquering intelligences did not deign to concern themselves It remarks that the harm which these conquests can do to men springs from their neglect of what is essential in man And the problem set is that of such a reintroduction of the spiritual into material progress that it will cease to be overtly or covertly inhuman

The point is very well made by Albert Camus in his recent book *l Homme revolte*

"It is useless writes Camus to hope to go back on technique The age of the spinning wheel is past and the dream of a handicraft civilization is vain The machine is only evil as it is used today We must accept its benefits even if we refuse its ravages The lorry which the driver drives day and night does not humiliate him, for he knows it to its last screw and uses it with affection and efficiency The real the inhuman exaggeration lies in the division of labour But by very reason of this exaggeration the day will come when a machine performing 100 operations supervised by a single man will turn out a single object This man will have to some extent rediscovered on a different level the creative force which he had as an artisan The producer will thus draw nearer the creator "

This is however a somewhat timid hope which relies principally on the evolution of machinery for the liberation of man Is there nothing better man can do on his own initiative to reconquer his autonomy and dignity? The soulless matter under whose tyranny he has fallen only exerts this domination over him because he has erroneously animated it with an intellectual force which is soulless too Just as God

man in His image, so man who has set up as the god of the modern world has built in his image the machine to which he has delegated as much as he has been able of what he believes to be his divinity The robot whose formidable power has finally turned against the man god from whom it derives is in this sense comparable with the angel Lucifer, whom God had made His chosen creature and who turned against his creator

Behind the present day drama of the West there therefore lies the fact that Western intelligence has gone astray has lost its soul or has at any rate overlooked it But once we come to examine this aberration we shall be forced to face the fact that what we are calling in question is nothing less than the civilization on which the West has lived for four centuries, that is to say the humanist civilization

This fact has already begun to be perceived by certain thinkers who have set forth the present day problem of the West in all its implications and in particular by André Malraux, in his latest books *Psychologie de l Art* and *Saturne* Seen from this standpoint, the birth of humanism, at the period which arrogated to itself the name of the Renaissance, was the birth of the man who dreamed of reigning over the world by his own unaided faculties and in particular by the supremacy of his intelligence Thus Leonardo da Vinci was hailed by Michelet as the man who was all powerful in all things This was the first step on a path on which one more step was taken in the eighteenth century when man relied for the exercise of his supremacy on abstract and disembodied reason It is no doubt true that the humanist West did not lose its soul straight away What it did do straight away was to break with everything there had been of spiritual force and of expression of that force in previous civilizations for it set up the principle of a progress which derived its inspiration and all the potentialities of its development from human reason alone With this principle Western man introduced into the world—which has not yet got rid of it—the idea that everything that is early is "primitive and everything that is modern represents progress By so doing he dated the beginning of civilization from the moment when human reason began to exercise itself and relegated into a world of artless stammerings everything in earlier times that was not or did not appear rational

Immense spiritual civilizations were jettisoned in this way for the simple reason that once the sovereignty of reason had been thus established the kingdom of the soul was closed

A remarkable example of this aberration is provided in an observation by Aurobindo, whom I shall quote again here This observation which is to be found in the introduction to *Hymns to the Mystic Fire* (Pondicherry 1946) relates to the misunderstanding of the Veda by Western rationalism and it demonstrates excellently the extent of this misunderstanding

The tradition of a mystic element in the Veda as a source of Indian civilization, its religion, its philosophy its culture is more in consonance with historical fact than the European scouting of this idea Nineteenth century European scholars writing in a period of materialistic rationalism regarded the history of the race as a development from primitive barbarism or semi barbarism with a crude social and religious life full of superstitions, by means of the growth of civilized institutions manners and habits thanks to the development of intellect and reason, art philosophy and science and a clearer sounder more matter of fact intelligence The ancient idea about the Veda could not fit into this picture, it was regarded as rather a part of ancient superstitious ideas and a primitive error But we can now form a more accurate idea of the development of the race The ancient more primitive civilizations held in themselves the elements of the later growth but their early wise *men were not scientists and philosophers or men of high* intellectual reason but mystics and even mystery men occultists, religious seekers they were seekers after a veiled truth behind things and not of an outward knowledge The scientists and philosophers came afterwards they were preceded by the mystics and often like Pythagoras and Plato were to some extent mystics themselves or drew many of their ideas from the mystics "

These remarks are so fair and so penetrating that they will help us finally to find our way to the solution of the crisis thus defined

It is in a word a crisis of humanism

Modern man who has lost control of the inventions to which his brain gave birth has been compared to the sorcerer s apprentice The comparison is wrong Modern man is neither sorcerer nor apprentice It was he himself who drove to its

logical conclusions a mastery which he craved and claimed that of a strictly rationalist and materialist science which he had developed in a field severed from all spiritual roots By so doing he showed up the insufficiency of the culture of which this science was the crowning glory a culture too narrow, too sweeping in its claims to absoluteness in its domain, to deserve the title of humanism which it assumed

What Western man has been calling humanism for four centuries has been the urge to become master of himself and of the universe by the exertion of his intellectual activity isolated from the rest of his life He has thus asserted simultaneously his claim to universality and his capacity for achieving it *by a deliberately limited selection of his faculties* What he has called the domain of the complete man has been the contemplation of the entire world by man restricted to a part of himself We must relinquish this error if we are to set humanism right and widen its meaning

There is no question of destroying it, any more than there is of disowning the achievements of science, which can indeed be set to its credit Western humanism has been at certain periods and in certain places, the field of those human achievements which retain their outstanding value But what we can no longer allow it is an exclusiveness which limits the conditions of man's future to the domain which it has arbitrarily elevated into the kingdom of man If the word *humanism* connotes the homeland of the human spirit then humanism does not date from the sixteenth century Mediterranean Europe is not its sole and permanent seat, nor is its only source a certain idea of Greco-Roman antiquity which, particularly as concerns Greece corresponds less to the total reality of the classical world than to a picture of which Renaissance man saw the lineaments in his own mirror On the other hand, once present day Western humanism is placed back inside the boundaries which must beset it the crisis which confronts it today will cease to appear either as unexpected or as an inevitable catastrophe The calamity would only be absolute if we persisted *in regarding the prestige of human reason as absolute too* But man today has turned from this inordinate and outdated claim to a complete consciousness of his truth and of his energy

After four centuries of man s efforts to break down everything and first of all himself, by analysis, he is coming back to

a synthetic approach to being reanimated by the soul With that approach, every value in every part of the world and in every period of the world s history, recovers not only its use but its place in an ordered hierarchy Whether such values come from the East or the West, they are no longer rivals but converge towards this new humanism which leads towards universality not in virtue of some questionable claim but of its own inner logic That comes out clearly in the passage from Aurobindo quoted above What he says of the Veda agrees with what Simone Weil says of Romanesque art with what Alexandre Varille has discovered of the religious philosophy of ancient Egypt and with what Marcel Griaule has revealed of the religions of Negro Africa

There is no question of confounding these various spiritual civilizations in a hotch potch of improvised equivalents The impulse that is needed today is one that will free the life of the mind from the limits within which the Western outlook has so long confined it The essence of the new humanism will be that in it the methods of life and of work that Western intelligence has been able to master will be employed in the rediscovery of long abandoned spiritual domains Thus intelligence, instead of exposing mankind to the risks that result from its presumptions and its encroachments will need all its alertness and its strength to serve the cause of a man who will be really complete this time not a man sidetracked into the material by the cerebral but a man who will be united body and soul, in the bringing of his own mystery before his consciousness

We believe that if a humanism such as this were to become a reality, East and West would find that much that separates them would disappear and everything that unites them—and unites the whole human race—would emerge All the grounds of the disagreements and misunderstandings which we discussed at the beginning of this paper would be done away with It would then be seen that the necessary condition of any real liberation of the Eastern peoples was the general liberation of the spiritual nature of man—a liberation which is no less necessary for the West

In conclusion let us face the fact that what is in question is a profound revolution The West—through the French genius in particular—was already committed to it in the first half of

the twentieth century by the significant direction which the most outstanding and original of its writers, poets, artists and scholars had taken It is none the less true that certain habits of thinking are not too easy to disturb and that certain re classifications of values may come as a shock That is perhaps a further reason why international, inter continental and inter confessional leaders of thought should unite their efforts with a view to reaching together the spiritual bases where the common truths merge

The Conception of Man East-West

by

JACQUES RUEFF

WHEN embarking on a comparison of the different conceptions of man as between East and West, the first question that arises is is there a difference in kind between Western man and his Eastern counterpart particularly as regards their thought processes?

All Westerners who have worked with Orientals will reply without a moment's hesitation that, save for a few minor details, the mechanism is the same Given identical educational and cultural conditions, the Oriental will react in precisely the same way as the Westerner His reasoning apparatus , in particular exhibits the same characteristics and produces the same results

Are we then to conclude that there are no differences on the spiritual plane between East and West? That would in my opinion be making a serious mistake

It is my belief that there is a profound difference of approach towards certain basic questions—a difference due not to any divergence in the mental process but to the fact that "idea groups on which the two civilizations are based have from a common point of departure evolved along different lines [1]

By common point of departure I mean the basis for the meditation of man who before discovering the physical world discovers the world of his own thought

It is, I think, indisputable that ancient civilizations for all their brilliance concentrated more on the inner being of thinking man than on the external world The thinker wholly absorbed in his own thought closes his eyes to the outer world in an effort to wrest from the immutable essence of reality the only true knowledge the knowledge of the suprasensible

[1] I have borrowed the notion of idea groups from the mathematical and statistical sciences, and in particular from *L'Homme Microscopique* by Pierre Auger (Flammarion)

world The matter of his knowledge is derived from divine revelation or from the ideas the Creator has made accessible to his intelligence

Was it not Aristotle who described thought as ' the thought of thought , and Clement of Alexandria who said that perfect knowledge appertains to that which is outside the cosmos that which is apprehended by the intelligence alone, and to things even more spiritual than these ?[1]

The philosophical and metaphysical systems of both West and East—and also, to this day, of all primitive peoples as well —rest on this basis, of things directly apprehended

The resulting mentality elaborated and systematized, attains its fullest expression in the West, in the theories of Aristotle and the medieval scholastics

The Aristotelian physics of medieval scholasticism, writes Gilson give an exact description of what the universe would be like if our sensory and emotional impressions were concrete objects, they represent a systematization of the error of our early years in assuming that our confused mental impressions, just because they are neatly named, described and classified like concrete objects, are in fact real forms or real qualities [3]

It is thus that the theory of the ego akin to the cosmos and sometimes even identical with the cosmos is elaborated, and this skilfully developed theory, based on strict logic and rational metaphysics seems alike to West and East, to answer their questions and allay their anxieties

But as time passes Western thought, almost unperceived by its proponents undergoes a measure of transformation For on the rich soil of scholasticism has been sown (tentatively by Judaism, then triumphantly by Christianity) the seed of a new theory the theory of human independence and responsibility

The seed sprouts and develops into the conception of man as being one indivisible and immortal, distinct from the surrounding universe claiming his identity in and even as against, that universe (or rather against its temptations), and accountable for his actions to God

It is in St Thomas Aquinas that the fullest expression of free

1 VI Strom 68
2 See Lévy Bruhl *La mental té prim ive*
3 *Etude sur le rôle de la pensée médiévale dans la formation d sy tème ca tésien* (p. 170)

and independent personality is found That being is called free, he says "who is his own cause We are acting freely, therefore when we act of our own accord—obeying the dictates of our will It is in this way he adds elsewhere, that God invests his creatures with the dignity of cause

Since he was distinct from the world and invested with "causal influence it behoved thinking man to take thought for the mechanism of his judgments and their effect on the "things on which they were brought to bear There thus originated the double current leading to Descartes and Bacon, the first completing the mechanism of the reasoning machine, and the second gearing it to the external world so as to render man powerful and capable of effective action

With Cartesian philosophy the detachment and liberation of the human personality are accomplished

The reasoning faculty is not something acquired or appor tioned, it is inherent in human nature The power of judging well and of distinguishing between the true and the false is something that all men possess, in equal degree '

This power is not something that man has learnt from the world He brings it with him he alone can exercise it No one said Descartes can understand save I

The glorification of reason is the vast and wonderful harvest reaped from the scholastic age

But this was not merely an end it was also a beginning While the reasoning mechanism was slowly developing thinking man was gradually ceasing to look within himself alone Another error says Francis Bacon "arises from ex cessive respect for and a kind of adoration of the human intellect, leading men to abandon the contemplation of nature and experience and to wallow instead in their own meditation and the fantasies of their own imagination [1]

With Bacon the reasoning machine begins to be geared to tangible phenomena It discovers that it can deduce them from a few simple principles which it takes as the premises for its syllogisms Thus, unbeknownst to the scientists of the day, modern science assumes its true character

Reason represents in fact a supreme effort to provide a logical explanation for all the phenomena apprehended by

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1 *De Augmentis* I par 45 *Novum Organum* I 48-? 79-114 and Preface of *Instauratio Magna*, p 190.

our senses It does not discover causes, it invents them, and by so doing it substitutes causation for succession in the world it presumes to call external

From that point, man s position in the world undergoes a complete change He can now, on the basis of a few simple propositions definitions axioms and postulates, deduce the entire system of tangible phenomena And the fact that the premises were originally elaborated in an effort to deduce cause from effect considerably facilitates the inverse process of predicting effects from causes

Working with premises such as these man is able to predict the interaction of tangible phenomena and so to control and utilize it Though he still sees the world as external to him, it is now subject to his will from being its slave he has become its master The device of experiment has given him power over the world such as he formerly exercised only over his own thought

And man looking in amazement at the extent of his power over the external world is so overwhelmed with the material results of his triumph that he forgets the nature of the methods whereby he attained his ascendancy

The age of "science triumphant has been ushered in Man, in the flush of his newly won power forgets that the under lying causes were invented by him, and for his own purposes He persuades himself that he discovered those causes and that they furnish an exact description of the world around him He forgets in his intellectual pride, that the premises of his syllogisms will convey reality to him only in so far as the tangi ble phenomena of the physical world are interlinked as the propositions in his mind are interlinked He assigns absolute and universal value to explanatory devices that are in fact purely man made

This is the epoch in which the young Renan wrote that science is useful only in so far as it investigates truths claimed to have been communicated by revelation [1]

Thus the era of science mongering and materialism" was to mark a deep divergence between Western and Eastern thought such as might have reflected in some sort the great dispute about "universals The West in its rational imperial

[1] L avenir de la science p. 32.

ism displayed a naive, absolute realism akin to that of a child who attributes reality to myths, quite forgetting that they are of his own making

Yet this very naivete was a source of strength, and for nineteenth century man the rationalist illusion proved the most fertile of human errors

It is true that the heyday of the youth of science was short lived It was not long before the genuine scientists reflecting on their science, discovered its limits, and very soon Western thought returned to its sources

Listen to the words of Emile Bréhier one of our foremost historians of philosophy I had the good fortune to embark on my career as a philosopher at the end of the nineteenth century, a period of lively intellectual activity It was the time when the cramped notions of science were being discarded together with a bankrupt spirituality compounded of pious hopes and high flown phrases a supreme effort was being made to revert to fundamentals in all activities of the mind—in science and art, religion action and contemplation alike It was the age of pragmatism, modernism and the philosophy of action, and of the revival of an intellectualism meditating on man s practical activities This movement was dominated by the thought of Bergson who taught me along with all my contemporaries, to realize spirituality and to understand it not merely as a set of conclusions deduced from experience by a process of not wholly valid reasoning but as the expression of a life *directly* apprehended [1]

Nor was this return to methods of the direct apprehension of knowledge confined to philosophy

Henri Poincaré who as a mathematician was at that period making a study of space and time expounded a sort of philosophy of the continuous , concluding "This shows that logic alone is not enough, that the science of demonstration is not the whole of science and that intuition must still act as a complement I might almost say a counterweight or antidote to logic [2]

This is the period when art is throwing off the shackles of classicism and Marcel Proust is experimenting with a new

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1 *Comment je comprends l'histoire de la philosophie* Emile Bréhier 1 *L'Année philosophique* Presses universitaires de France Août 1947

2 *La valeur de la science* p. 23 (Flammarion)

language, trying to suggest rather than describe the unbroken continuity of the psychic life of his characters

To speak therefore of a conflict between Eastern and Western civilization the former resting on profound spiritual values and the latter living by the arid light of reason in action, seems to me to be an oversimplification

The Westerner knows that, if science confers power, the reason is that it was created to do so He no longer believes, however, that it reveals the real underlying nature of things He knows that if things exist it is only their reflection in the mind of man that he is able to apprehend, and that the nature of this reflection depends on the mirror as much as on the object reflected

Thus the West has proceeded from its raw, young and (because of its youthful self assertiveness) ill informed science to a science that is better informed It has reverted to intuitive, direct knowledge from which the East had never departed

Western civilization has added thereto of course, scientific discovery and creation, which feeds on its own power and is expanding constantly before our eyes

But the East also desires to possess the power of science and the methods we have applied to achieve it can equally well be adopted by the Orient

Thus there is a place for science at once humble and majestic in the new system of human knowledge in the East as well as the West

There will still be differences of shading between Eastern and Western thought but there is no longer any dividing gulf The two are linked together, and now advance side by side—each retaining its own inherent characteristics—building the road towards the great horizon of a real civilization

The East and the West

by
HILMI ZIYA ULKEN

EAST and West are two entities in which within the familiar frameworks there is a whole variety of manifestations each of which has evolved sometimes on parallel and sometimes on diverging lines The basic backgrounds are however, so different that it is the coincidences that strike us when we see them, and one is tempted indeed to say that there is no such thing as common types of humanity Their existence is nevertheless attested when we look at social life or at the ideals of communities It is therefore not only in human ideals but in life as it is lived that the bases for a *rapprochement* between East and West must be sought

It was the sense of moderation and precision that underlay the fine reputation of the West but the latter abused its powers The East for its part was inclined towards meditation and took refuge in an escape from reality The result was that the two halves of the world became indifferent to each other and this state of things has lasted for centuries There is admittedly a certain tendency of the two worlds to "come together , but it has remained in a number of respects only a tendency There are certain ways in which they do understand each other, the East is aware of what it lacks and wishes to modernize itself by adopting European civilization Although various interpretations of modernism have been suggested we can say that all Orientals aspire to the benefits of present-day civilization, they want to initiate themselves into the scientific outlook of Europe And the movement has not been "one way" only The West, in seeking the reason for the present moral crisis, tends to look for it in the training which present-day man receives We find a fairly strong movement against the debasing of culture and this movement enables us to discover points of contact between various forms and aspects of man

This tendency, which is sometimes aided by a taste for what is foreign to our normal environment and by a measure of attraction to cultures other than our own, entitles us to hope that within a comparatively short space of time there will no longer be any real tension between East and West, or two mutually incompatible aspects of the human race

II

There was a moment in human history when no such distinc tion existed At that time there were three separate circles, each with its own civilization—India China, and the Middle East Of these the third based on Egypt and Mesopotamia, expanded into Greece These three worlds developed along parallel lines they each had their great genius–Buddha, Confucius and Socrates, and they arrived by the same pro cesses, at the same results They had passed through the stages of mythology, hylozoism sophism, and the discovery of the conscience Conscience had meant, for India, delivery from pain through mortification for China, the practical ethics of filial piety and for Greece rational ethics transformed into a metaphysical system The Greek civilization, then moving away from the other two gave birth to Western civilization, collaborating with Christianity while Islam, a delayed religion which came upon the scene some six centuries later than Christianity became one of the first manifestations mili tating in favour of a bringing together of East and West

III

A century ago, Turkey was making the first experiments in *rapprochement* with modern civilization For the eclectic Tanzimat , in the first place the distinction between East and West was a distinction between soul and body quality and quantity The outlook of the Tanzimat which was a reformist movement reflected, with us, the ' dualist thought of the nineteenth century Was this a fortunate circumstance? *It is very definitely open to doubt*

For other quarters the West merely represented the material ist outlook it was the East that held the keys to the world of the spirit The Western outlook it was held, originated in an

ambition to conquer nature, the East was regarded as given to mystical thought, that thought gradually detaching itself from the tangible world through its own particular symbolism This dualism , a more or less reactionary conception was followed by powerful evolution in a more Western direction

The new outlook drew the distinction between East and West by suggesting that what was dominant in the West was the human personality", its social order being based on the behaviour of free men who exercised personal initiative whereas in the East the individual was absorbed by the community *This distinction was based merely on the different* forms of training received by the two types of social man, although it was simply a question of different natural factors, man could influence the circumstances of his environment and transform his position by dint of social research and of education (Prince Sabaheddin)

Dualist thought finally led to an attempted reconciliation between Islam nationalism and the West Underlying this attempt was the drawing of a distinction between culture and civilization Culture was of Eastern origin, whereas civilization was seen as the aim to be attained—in fact the West The distinction corresponded to that between content and form Dualism—the difference between the two worlds—was thus reduced to culture and civilization (Ziya Gokalp)

The last available means of finding a solution consisted in the radical adoption of European civilization This meant that there was only one dominant civilization about which there could be no discussion Culture and civilization were one and the same thing If one was baptized into a civilization that meant adopting all its virtues and all its vices No discrimination was possible nor could any compromise solution between East and West come about For the Eastern peoples Westernism was an inevitable development This was the revolutionary movement initiated by Atatürk

IV

We are now faced with the following problem Science in the past century claimed to regard man as an animal but in fact man instead of adapting himself to his environment creates his own world He needs a long process of education in order to

assimilate the experience accumulated by past generations From this stems his capacity to acquire experience—his his toric being He becomes a social being only after a long period of education Thus, man may be defined as an educated being and hence as a being who has not only mastered but actually created the world of values

Throughout this period, man s activity is the complete opposite of that of the animals (a) he projects himself into the future, and evolves his ideals (b) he projects himself into the past through the constitution of his memory and his personali ty and (c) *he projects himself into space and reality evolving* his tools and his concepts The stage of *homo sapiens* precedes, therefore, that of *homo faber* Attitudes translate themselves into activities whereby his individual personality is formed, these attitudes are, in ordered progression escape from reality, the discovery of values and the creation of techniques There are several techniques each of which corresponds to a given value aesthetic technique for aesthetic value, vital technique for vital value and so forth

An essential feature if not *the* essential feature, of man is the battle against himself it is seen, in every civilization, as self sacrifice There is no single anthropological type that does not possess this feature Man may therefore be defined as a being who creates himself by sacrificing himself On this point it seems to me East and West are agreed It is not the intellect and free choice that distinguish man from the animal, since their origins can be traced to the animals Man s nature has its roots in a principle at variance with life and its evolution—*the spirit Man lives not in a local environment but in the* world Human attitudes come from right within the individ ual they take shape when some propensity or other is re strained This notion must be supplemented by that of man s concrete unity The notion of duality has served to signify, in some sort, a battle between two universal principles, in which man is the setting for a regular inner drama

It is certain however, that the human being s consciousness of restlessness goes or comes, before axiological duality Instead of seeking for sublimation in the struggle between opposites that are stronger than man himself and in regard to which, therefore he is heteronomous it is better to start from the restlessness that the concrete being man feels as to his

destiny and his existence in the world—*from which we are led to his resistance against himself* and hence to the two aspects of his being which we call body and soul

We thus arrive at a conception which first of all postulates man s autonomy *in his unity and then proceeds to what is* "bivalent in him and to the ways in which he is, physically and spiritually, externalized

Man s concrete unity, with its indefinable properties, distinguishes him *from other beings not by the evolution or the* combination of those properties, but by his own progress towards *autonomy*, as compared with other beings

V

Let us follow out the stages through which man has passed throughout his history

Primitive man lives not apart from other forms of creation but within the whole, projecting his troubles and inner conflicts *into it His mentality is pre logical in all its primitive* purity, later it will be invaded by reason and conscience

The three circles ' of civilization *evolve in the same way* Greece aims at what is intelligible logic being regarded as the key to all problems *Man is distinguished from other beings* by his intellect This is the period of humanism and of the intelligence The sovereignty *of man is born but, at the same* time, his servitude Aristotle s Organon which begins by being the means becomes later, *the end*

India has discovered conscience with a view not to "rationalizing nature *but to unfolding the world of the spirit* Christianity and Brahminism are alike concerned to save man who has fallen *from his supernatural state* and to deliver him from his sin through sacrifice of self they establish the same conception, based on the Trinity and the incarnation to find the union of the natural and the supernatural worlds in the miracle of man But Hindu mysticism finds expression in over emphasized, concentrated spirituality, whereas with Christianity the effort is in the direction of moral authority With the Yogis union with God—the control of the body through breathing—leads them back to their primeval origins

The mysticism of Islam and that of India have certain common features Islam concentrates on collective ecstasy,

the mystical practices which lead to the communion of souls, detachment from self and union with God through an in creasing process of spiritualization—the dialogue between the soul and God This dialogue ends in a union (*wusla*) in which the two entities are fused and become one Real spiritual union is achieved

China, reaching the stage of a feudal empire based on the supremacy of the patriarchal family, had discovered the ideal of "unchanging man within the framework of sub mission by the inferior to the superior

Greece enthroned the intellect, identified it with the super natural world and substituted it for the mythical gods She evolved what was known as the sage who lived in harmony with the natural order of things subjecting passion to reason The influence of this type of being was most felt in the reconciling of his thought with what Christianity had to offer The conflict between the Greek *Logos* and the Christian *Verbum*, between reason and conscience between justice and charity is resolved, in European civilization into a synthesis—though reason and faith cannot always adjust themselves to each other completely, and one or the other will be subject to some measure of constraint

Islam, coming some six centuries after the development of religious man formulated a universal law, based on sub mission to the divine will and shorn of all anthropomorphism Here, man possessed only that conditional freedom accorded to him by divine grace Iconoclastic Islam concentrated on the purification of the soul, it proclaimed itself the saviour at once of the conscience and of social life, through its legislation (*Sharia*) The prime feature of Islam was that it reconciled life on earth with the supernatural It therefore drew rational arguments from Hellenistic thought The ascetic was the "perfect man who linked the visible world (*alam al ṣahâda*) with the invisible world (*âlam al gayb*) The important point is however that the "*fana fi al haq* (annihilation in God) is not for the Sufi a conclusion, but a transitory stage to the *Baqa bi Allah* (perennialization", or everlastingness in God) and to a return to the world The Sufi is not merely a man who seeks his own salvation he has a teaching mission, and is therefore akin to the Fathers of the Christian Orders All these ideals—except that of Greece—were based on the conception of *sinful man* expiating his sin through sacrifice

VI

In Europe, despite various attempts at synthesis, the antithesis between man of the *Logos* and sinful man created an unstable position for the soul In it, we can see the beginnings of the West's loss of serenity By what it erected artificially, the West departed from nature, accordingly it began to look longingly back towards primitive man Western man retired into himself where he had dwelt for so long, he therefore lost all contact with other men, or made contact with them only on the purely conventional plane As a result, he was driven towards the man of the mind Modern man finally ended by becoming an egoist without ideals Thanks to the development of natural science, he created the type of man who is a "denier First he denied or renounced his past his position in the world, and his destiny He destroyed the scale of values he gave himself up to ambition through which he thought to discover the remedy for all the evils afflicting him But this negative attitude merely led him by way of reaction against his negativism, to regard himself as the creator of values From this he presumed to treat others not as human beings but as instruments This conception of man which is only justified to the extent that man degrades values and is proclaimed by materialist régimes at the expense of every human ideal is today in a social and ideological *impasse*, and the result is an ever greater desire to discover total man by supplementing what is lacking through drawing on other types of humanity hitherto ignored and despised Since the human being's dominant feature is his *historicalness* present day man can look back on past human experience experience gained in varying situations by different civilizations and he can take as his ideal "total man partaking alike of the deep thought of the East and the technological power of the West

VII

History records several attempts to close the gap The first was Greco-Buddhism the second was Manichaeism and the third was Islam with its effort to reconcile the "eternity" conception of Greece with the "creationist" conception of the Semites Finally both Japan and the Ottoman Empire sought

to bring about a fusion of European civilization with the mind of the East

Today, Turkey and certain other countries of the Middle East have rejected all compromise They stand out resolutely for modernism, and do not see how they can become modern, independent nations unless they adopt Western culture The reforms involved are all essential to any people on the thres hold of modern civilization No satisfactory solution will ever be found through the adoption of out of date compromises The Eastern nations however, having modernized themselves *by the necessary reforms, must resuscitate the values of their* past and bring them into play in their contemporary life They need not adopt out dated habits and customs what matters is that the spirit of a nation should make its mark on modern civilization True nationalism can only come about through an original interpretation of the civilization adopted Clashes of national pride however, instead of creating new values, prevent the cultures of the nations involved from exercising a mutual influence upon each other The Eastern are just as capable as are the Western peoples of imposing on the modern world their ways of feeling thinking and acting The diversity of these interpretations is not merely the foundation of the nations independence it is also, for the ancient civilizations, the spiritual serum that will rejuvenate them

The true reasons for the lack of interpenetration between the two worlds are to be found in an endless series of prejudices To these obvious obstacles may be added the views so often expressed as to the multiplicity of closed cultures—the impossi bility of penetrating them the clash of patriotisms, belief in the decadence of ancient peoples etc

Cultures however, are not closed circles They are brought about by interaction between different human societies The greater the scale of *such relations, the more comprehensive* the civilization tends to be If the ties slacken or are broken the civilization becomes static and a scholastic period is ushered in

Every cultural area seeks an outlet for its spiritual and *material produce But the countries that purchase that pro*duce imitate the others creations only for a period of appren ticeship, they end by becoming skilled creators themselves The cultural centre of gravity shifts, the limits of the culture

expand, and the supplying country itself becomes an outlet Many inventions are reviewed some become obsolete, but many others are maintained The rivalry set up between the supplying nation and the client or customer nations takes on in some sort the form of a conflict between totalitarianism and liberty The supplying country resists so as to remain the centre The ancient system withdraws into itself it becomes a tradition without progress pride in the past bereft of all sense of reality

Ancient civilizations can spread (a) along the great natural channels of communication, (b) by movements of population on the occasion of wars and migrations, and (c) through the growth of world religions

It is not only that modern civilization *permits* the various nations tendency to rely on their political and cultural autonomy, it actually *facilitates* that tendency Our present civilization not merely consolidates nations it also creates them It brings them to birth by both positive and negative means (a) by the need felt, on the regional level for technological improvement (b) by the spreading of democratic ideas which inspire not only the privileged but also the under privileged to claim their independence (c) by the development of public education, and the cultural emancipation of native languages (d) through romantic and nationalist movements inspired by their European antecedents, and (e) through a reaction against domination by the powerful European civilization itself a product of democratic ideas brings to birth other nations similar to its own

The human being is the product of education and education likewise, is the surest means of bringing the East and the West together

Education in our view means two things to draw instruction from the treasure house of culture with a view to succeeding in life, and to live in harmony with our being and in close association with our fellow man

Each civilization has evolved some plan whereby these objects of education can be achieved Our own period which is that of a world civilization consisting of the original cultures of all nations needs an education that will be national in character This must be based not merely on Greco-Latin humanism but on a wider type of humanism, compounded of

understanding between all the cultures of the world Each country, as an independent member of this world civilization will contribute its characteristics and view of life to the ‘symposium of nations What is of interest to us is to note the varying but also the complementary features of the peoples concerned If cultures are isolated, certain exaggerations result, one culture or the other may become hypertrophied or atrophied as the case may be But the educationist must observe such undesirable developments so that the necessary improvements may be made to the educational system Very occasionally, also the two aspects of education that we have mentioned change their relationship the first one becoming dominant if not exclusive and that is the symptom of a crisis in culture Such is the crisis we are now witnessing, some consider it is merely a temporary crisis, while in the view of others present day civilization must seek for remedies outside itself

In the East education was based on the development of the inner life—on spirituality In India the Yogi sought it through the practice of meditation and concentration In the case of Islam, the Sufi identified it with the acquiring of mystic virtues so as to consummate union with God and to return to daily life with a teaching mission Hence the process—with Ibn Arabi for instance—of *Uruj* and *Nuzul* (ascent and descent) The object was simply to abolish the ego and egoism by means of the alter ego in communion with the spiritual realm through a process of auto suggestion

In the West education was based on development of the intellect—that is to say simply on instruction But the reaction against scholasticism gave rise to the experimental method, and then to the active method In this system, the dominant factor is the will what takes place is a consciously directed *effort* brought to bear on the outer world

Auto suggestion acts through the subconscious, and by means of the nervous system in the case of will and effort the muscular system is involved It is a case of two complementary yet opposite processes of the human organism to the extent that we use our will suggestion is thwarted, since an imposed effort instead of leaving the field free to auto-suggestion produces a counter suggestion Similarly, if we relax so as to let an idea take root in the unconscious mind, our will is never called into play Yet will and suggestion so far from

replacing each other, complete each other, in our make up by their mutual activity Action unaided by suggestion will lead to fatigue and exhaustion, which will destroy soul and body, suggestion unaided by will infects the mind and renders the body abulic and ineffective for the purpose of any human activity

In an autonomous' man, these two activities complete each other and make him into a person Any abuse of his autonomy, on the other hand, impairs the functioning of one or the other process, as the case may be Yogists and activists continue to uphold opposite theses, each of which, by itself is inadequate Despite its exaggerations in the one specific direction, the West has discovered the laws of auto-suggestion it has tried to apply them, and has admitted the drawbacks of its tradition whereby the mind is directed towards the conquest of nature The East has practised auto suggestion and its accompaniments for tens of centuries and has even abused them, to the detriment of its own material success The educator, without stooping to a compromise, can take man as a whole and suggest a form of education embracing at once the heart, the reason and the will The Cartesian method though seemingly irreconcilable with the finely intellectual method of Pascal, must have its place in the education of the future

Eastern education leads us to the authentic" being its aim is therefore, identification with the spirit not external manifestation with regard to others The mystic is led by his "inner dialogue towards the abolition of his superficial self and towards the discovery of his deeper self, his *huviyya* Western education on the other hand, leads to what *appears* and therefore seeks a form of expression that can be understood by others

In passive education, there is no fusion between being and appearing, being, in man requires certain things that his appearing cannot provide Such education is accordingly apt to create false personalities, its consequences are despair hypocrisy and morbidity Under a process of active education on the other hand, the individual at once enters into relationship with the world he penetrates into its innermost corners, he creates it Because others cannot penetrate his conscience, modern man has to form a contractual association with them An open conscience brings about spiritual reciprocity This fact was noted from the purely sociological standpoint by Le Play and Tonnies but if we look at it from a wider point of

view we see in it the two complementary aspects of human existence

In the philosophy of education, two separate conceptions must be noted (a) education that has to do with ideal values, that is designed to implant in children the ideals of man, (b) education that has to do with social realities Every period, every social group, has its real types of man These types however, are not all provisional or variable under differing conditions Given types, though stemming from different civilizations or cultures, have certain common features There are craftsmen, warriors, priests traders, peasants town dwellers, neighbours and relations in every group whether it be large or small primitive or developed, ancient or modern—in short in every form of society Though the human groups themselves may change, these types retain their essential features The education of a craftsman a priest or a peasant is conducted on basic principles which are common to almost every civilization There is nothing therefore, to rule out the possibility of an autonomous science of education and of its use even subsequent to a change in social conditions The types in question are so many that it is impossible to calculate the number of subdivisions existing within a given caste, or within a given group bound together by ties of blood or material interest It will be the educator s task to study, in the first place the essence of a given social type, it will be the task of the sociologist to explain the variations that flow from differences of time and place

In his detailed study of social groups, the educator will enlist the aid of the sociologist No educational method can be applied effectively without a clear idea of the structure of the society involved Education of the future can be based on an understanding between East and West only if a thorough study is made of each human group existing within that general framework

ADDENDUM INTER CULTURAL RELATIONS BETWEEN EAST AND WEST

I should like to make a brief reference to the cultural and philosophical relations that have existed between the two

worlds in the past I have already mentioned the influence of Alexandrine Hellenism on Hindu thought Greco-Buddhist culture in the first place (at the time of King Asoka) and then Greco Bactrian culture had produced works that were a cross between two civilizations, and Pali Buddhism had been accepted more widely outside than within its native area The archaeological excavations of Van Le Coq Müller, Grün wedel Aurel Stein and the like, have revealed in regard to this civilization information most of which has not yet been properly studied

Through these scholars we have been acquainted, since 1914 with Manichaean Buddhist and Brahminical manu scripts that reveal to us the origin and expansion of these religions in Central Asia Manichaeism the successor to Baby lonian syncretism, embraced in itself all Middle and Near Eastern beliefs except Judaism, it comprised the ideas of the Christian Trinity, the Incarnation Brahminical transmigra tion and the duality of Mazdeism Its ideal of man—Burkan—spread, during the fourth and fifth centuries from Turkestan to Abyssinia and appearing within Christianity as a dualist heresy with the Paulicians Bogomils, Patarins and Catharists infiltrated by way of Byzantium to Rome and throughout the whole of Central Europe

Augustus during the first half of his life was subject to the influence of this religion Islam calling it *Zindiqa* condemned it though under Islamic principles all other celestial beliefs were respected the early Abbassid Caliphs however, who were free thinkers tolerated all opinions and sought to bring about an Eastern Renaissance, the Manichaeans therefore together with the Syriac and Jewish divines were protected in the palace of the Caliphs but this generous tolerance was soon to be followed by the condemnation of the *zanddiqa* For Islam regarded Manichaeism as its enemy by reason of the latter s denial of the one, universal and creator God, and because of its tendency towards communism But the influences exerted after Alexander by the Syrian and Jacobite schools paved the way to the century that was characterized by deep interest in the translations and commentaries of works and the interpretation of thought emanating from Greece and Hellenism Here Hindu influence should be mentioned though it was comparatively feeble

The period subsequent to the ninth century saw the flowering of Islamic thought Hellenic thought continued to be an influence, but there was added to it a blending of religion with peripatetic philosophy The theologians, however, very soon rejected all these conciliating tendencies Islamic thought reached its apogee with its scientific and philosophical production between the ninth and eleventh centuries, this activity spread well beyond Baghdad and established itself in such distant centres as Samarkand Al Kahira (Cairo), Seville Toledo and Sicily Arabic in the early Middle Ages, was the only language of the humanities, and apart from the nation of the Prophet Persians and Turks also took part in the scientific work Westerners, too, visited the Islamic institutions in Andalusia North Africa and Sicily, to imbibe knowledge Thus was ushered in the period during which were translated, from Arabic into Latin many of the Greek works—with their Arabic commentaries—and original Islamic works as well We may mention the names of Albatagni, Alhazen Alrazes Albubatur, Alkhorasmi Algorithmi Avenzoar, Avenbator, Avicenna, Alfarabi Gazali and so forth This tide had reached full flood by the thirteenth century when the Christian renaissance of the Middle Ages began

The two worlds despite the hostility engendered by the Crusades maintained their cultural and intellectual relations right down to the fourteenth century H H Schaeder seeks the origin of Ibn Arabi s perfect man in the Burkans of the Manichaeans for Corbin the genesis of illuminist thought (*Icharaqiya*) lies in the thought of Mazdeism M A Palacios traces the influence of Al Gazali down to Pascal by way of Ramrom Marti the Spanish priest who was inspired by Gazali (though he did not quote him) and who inspired Pascal in the same way When Frederick II, Emperor of Germany and King of Naples asked certain questions with regard to Greek philosophy Ibn Sab in replied to him in a well known book—*The Sicilian Replies* Finally according to Palacios Dante found the model for his *Divine Comedy* in Ibn Arabi s eschatological description of the mystical ascension (*Futuhati al Makkiya*)

As for India, the Persian influence was felt throughout that land through all the ages Islam s influence began with the invasion by Mahmud Gaznavi (1175 1210) Under the Turco-

Mongol emperors the regime, so far as religion was concerned, was extremely liberal, and Shah Akbar and Akbar Nama were responsible for the construction of a temple, each part of which was designed to be devoted to a separate faith There was, initially, considerable resistance to Islam in India, the polytheism and idolatry current there rejected Islamic monotheism The iconoclastic outlook of the Moslems and their aversion to the caste system, created an unbridgeable gulf between the two worlds, and Islam s real influence in India only began with the introduction of the Moslem Orders there (the Naqchiya Nurbahchiya Ruchaniya etc had found adepts not only among the Moslem Hindus but also among the Brahmins) Al Biruni s book on India (Kitab malil Hind) bears witness to this influence, where it speaks of Patanjali No human type was so close in appearence to the Yogi as the Sufi whose asceticism postulated the annihilation of self and the love of the divine Once it had come under the influence of Sufi ism India discovered in it one of its own ideals In copractice, the *fana* of Islam and the *Nirvana* of Buddhism coincided This current of inspiration was reflected in its last representative Mahatma Gandhi in the pantheism informing his *Saotyagraha*

Christianity infiltrated very slowly and conversions were very rare The Hindus regarded the West as the parent area of the invading missionaries" Even the modern reformers Tagore and Gandhi, crossed swords with the West and tried to instil into India attachment to native culture and the sense of a spiritual vocation Today, however modernism combined with the conservative Hindu outlook—though there is an irreconcilable difference between them—hold out the prospect of a national synthesis for the future

The West, after Alexander s initial attempt at "cultural invasion" made another effort subsequently—and vainly—with the crusades but much later on it discovered vast continents and outlets and conquered the entire world with the result that European civilization became world civilization Had the tendency towards invasion not been followed by a desire to acquire knowledge, the spread of European culture would have had no point As it was however the sciences of man were born and the natural sciences developed

In its intoxication with victory, the West let its judg

be coloured by pride The result was a variety of poisons in the shape of prejudices as to the inevitable collapse of ancient cultures, over estimation of the social ego race superiority (or superiority of part of a race), the inevitable evolution of humanity in a single direction, the denial of all values (by regarding them as out dated) a reversal of the scale of values, and the substitution of the values of hedonism for those of the mind

All the same it is the love of knowledge the pure scientific outlook—the fruit of so many cultural ties and the only valid heritage of past periods as a whole—that is best fitted to deliver the world all the world, from its moral crisis

The most radical stage in man s evolution is the transition from ethnic (national) religion to universal religion The establishment of celestial religions is the root of the individ uals autonomy as of secularization (the transition from the closed system of the sacred to the profane and to the pagan), it ushers in the sages, the prophets the saints laicization and the examination of the conscience

In this way the ideas of equality, brotherhood, justice and human freedom develop throughout the two continents We find the origin of our tetralogy in the world religions and this opens up the prospect of a universal faith, transcending all regional differences of form and ceremony in worship This ideal can be made a reality and placed on solid foundations by the nations themselves who are the creators of their own cultures That will never bar the way to world co-operation For humanity at its sanest will consummate this task by aiming not at some form of abstract unity impervious to social diver sity but at unity *in* diversity, leading the nations to one single ideal of man and to one single method of education

The Concept of Man and the Philosophy of Education in East and West

by

A R WADIA

THE basic document prepared by the Unesco Secretariat is actuated by the desire to evolve a philosophy of life which could serve as the basis for the One World ideal which lies at the back of the UN as well as of Unesco To its credit let it be said that it does not gloss over the differences between the East and the West and yet sees in the political and economic developments of today the possibility of the one civilization of tomorrow and seeks for guidance towards this end in the discussions it is intended to initiate at a high philosophic level

Before raising any philosophical issue it is desirable to be clear about the exact significance of the terms used—especially as they are apt to be so misleading, both in what they denote and what they connote As mere geographical terms East and West have a quite simple significance But when they are opposed to each other as cultural units there is inevitable confusion Every sociologist knows the effect of geographical and climatic factors on the development of peoples in particular countries, and we find characteristic differences between the different nationals of Europe as between the nationals of so vast an area as Asia comprising the Semitic Muslims the Aryan Iranians and Hindus and the Mongol Chinese and Japanese In recent years it has become fashionable to contrast the philosophies of the East and the West as if each stood for a simple entity The basic document does not commit this fallacy of taking for granted that the civilizations of the East and the West are just two different things It is alive to the fact that the culture of the Latin world is different from that of the Slavs, and that the Chinese culture is markedly different from that of India while Japan borrowing its religion from India and its culture from China has evolved yet another culture of its own which neither China nor India would care

to recognize as theirs The Middle East, predominantly Islamic has again evolved values of life markedly different from those of its neighbours to the East or West To the average Westerner the East stands for both India and China which are regarded as a cultural unit, though the attitude of China has far more points of kinship with the traditional West than with her next door neighbour, India Even eminent Indians are apt to look upon China as Buddhist when the Chinese themselves have looked to Confucius for inspiration rather than to Buddha and the degree to which they accepted Buddha was due to the ethical content of Buddhism rather than to its metaphysical content

The so called contrast between the East and the West really boils down to the contrast between Europe and India, for India has produced a metaphysics unique and unseen any where else While saying this let it be clearly understood that it applies mostly to Advaita Vedanta or Sankara, and not to all schools of Indian metaphysics If in the future evolution of one culture we have to make room for the contrasting philoso phies of the West and Advaitic India it is necessary to be clear as to how far and how deep these contrasts go

Western philosophy has always aimed at knowing the universe in itself and/or the reality behind it Knowledge for the sake of knowledge has been its motto through the ages and that is why till two centuries ago it made no distinction between science and philosophy In India on the other hand, since the days of the Upanishads there has been an emphasis on the *jnan* that leads to liberation (*moksha*) and that *jnan* is concern ed solely with the knowledge of the reality one abiding, unchanging Naturally the flux of ordinary life came to be looked upon as of no importance or only of passing importance for the day to-day world It has produced a sense of superiority to the world around and even an attitude of indifference so beautifully crystallized by Matthew Arnold in his famous lines

The East bowed low before the blast,
In patient deep disdain
She let the legions thunder past
And plunged in thought again

This is not mere poetry but a fact writ large on the pages of Indian History

This has given rise to another characteristic difference in the attitude of philosophy to religion If Socrates was the first in the line of great European philosophers he was also the first rebel against the priests and the traditional gods of his country He died a martyr, the first in the long line of martyrs in the history of Europe Scientists like philosophers have paid for their advancing knowledge with imprisonment torture and even death No such conflict has been seen in India Philosophy as an inherited creed has become a part and parcel of the religious tradition, with all its paraphernalia while science as a humble and a subordinate partner in the firm has never evoked any opposition There have been conflicts between rival schools, but rarely have they gone beyond verbal gymnastics, and if there has been religious persecution it has taken the form of excommunication of individuals or of families not so much for differences of creed as for breaches of caste rules Whether Advaita is strictly consistent with a theistic religion is a very big question which cannot be taken up in this short paper Suffice it to say that while relegating even *Ismara* to the world of *maya* in philosophic theory in practice the Advaitin has remained as religious as the more pronounced theists like the followers of Ramanuja or Madhava

If philosophy in the West ends in knowledge in Advaitic India as in other schools of Indian philosophy that knowledge as *jnan* must end in liberation from the cycle of births and deaths In other words Indian philosophy is pragmatic in character This liberation from the iron chain of births and deaths does not come easily It is an achievement of life after life a patient toil either of *bhakti or karma* culminating in *jnan* Philosophy is not an end in itself It is but a means to something higher i e the highest aim in life *moksha* This brings out a fundamental difference in methodology too for this highest knowledge is not won through logic or what the West has come to know as concepts It is a direct intuition, a *darshana* a vision of reality which is beyond words and therefore incommunicable It is mystical at bottom a matter of faith That is why in India there are numerous schools of philosophy and even more religious sects which fundamentally are based on the individual s faith in a teacher, who may be dead or alive

Then there is the fourth difference between the West and India Where religion is strong there is bound to be a greater

emphasis on its ritualistic aspect than on its moral aspect At the highest level the ethical precepts of India are inferior to none, but the joint forces of caste hierarchy, strength of religious faith, ignorance, with its close ally superstition, and centuries of political subordination have all conspired to put a premium on the conventional morality of castes

On the basis of these considerations one might be tempted to draw the conclusion that the East and West will ever remain poles asunder, as Kipling is supposed to have taught, though he actually taught something entirely different

> *But there is neither East nor West Border nor Breed nor Birth*
> *When two strong men stand face to face though they come from the ends of the earth*

Though one particular school of philosophy gives one an impression of an India whose feet are not on solid earth, but dangle somewhere in the clouds, there are other schools who do not look upon the solid earth as a dream But even if all Indian philosophy were to teach us to look away from the joys of earth as a dangerous snare there is another phase of Indian life which revels in poesy and song and dance, and in which stones and marble become endowed with sparkling life, while her kings have displayed a splendour that has become legendary in all the corners of the earth So there is a point where Indian culture cuts across the most secular learning of the West and challenges comparison point by point with the best economic, political and medical thought of the Western world

In the olden days when wide spaces high mountains and deep gorges divided one country from another it was possible for a culture to develop an isolation, which in its turn produced a sense of superiority and aloofness But while prophets preached the oneness of humanity and philosophers logically evolved a lofty universal ethic it is the scientific achievements of the last two centuries that have annihilated distances and brought the peoples of the world nearer one another than ever before Apart from what the physical sciences have achieved, the biological sciences and the social sciences have done much to break down the old ideas of racial or national superiority Heredity of course counts and plays its part but improvement in the environment has already done so much that it holds out a hope for a new humanity The protagonists of negro in

feriority could hardly have imagined that out of the wombs of slaves could spring such geniuses as George Washington Carver or Booker Washington, that in the space of a century negroes would produce leaders in every field of life The miracle that has happened in America can happen in Africa too as soon as the fiction of white superiority is exploded and the pressure of political repression is sufficiently relaxed to afford opportunities for educational advancement to the indigenous populations of Africa

Individuals will differ from one another but every one of them has a potentiality for good that needs to be exploited to the full—barring of course the limitations imposed by ill health or an unhealthy environment No factor in improving an environment is so important as improving education It is the mightiest lever for the improvement of mankind and the future of humanity is bound up with the question of education But before we can think of education on the right lines we should be conscious of its defects in our existing systems I am not referring to defects in mere methods of teaching These are questions of detail, of no intrinsic importance for even bad methods of teaching have produced good men and good scholars What I have in mind is something deeper the contents of our education The defects here are mainly three

Religious fanaticism of a virulent type is almost dead in all countries It may be due to the fact that religion perhaps does not play the same important part in our lives as it used to do In fact it is a common criticism that modern education tends to be godless at least it has been so in my country and among the educationists in India generally there is a deep mistrust of religious education inspired by a fear that it might give free rein to old prejudices and provide a fillip to antiquated notions which would ultimately do more harm than good In considering this question we have to be conscious of the fact that man is spiritual or religious at heart No less a person than Dr Robert Millikan a Nobel Laureate told leading physicists that a lifetime of scientific research had convinced him that there is a divinity that is shaping the destiny of man and he added "a purely materialistic philosophy is to me the height of unintelligence Far too often has religion in most of us taken a narrow view of man and God alike This has been

abundantly proved by the religious history of mankind Each onward moral step has led to a deepening conception of God and that in its turn has deepened the moral foundations of our life Nothing is so interesting as the study of the growth of religion in the world as a whole But most religious teaching in our schools and homes runs in a narrow groove, sincere perhaps but rather cramped No wonder that it produces in some a zeal to convert the world and tends to breed in others a supercilious indifference Real religion should produce in each a reverent consciousness of a transcendent and benevolent power irrespective of the individual modes of approach to that power in the form of worship Such an attitude can be developed only if even as children, our boys and girls are taught that God is one, and that all the prophets teach the same truth Such a training will develop a sense of tolerance and appreciation and a consciousness of man s journey in the quest of God, and they will begin to feel that a flame that has passed on its light to countless other flames must disdain so sordid a feeling as jealousy and identify themselves as fellow pilgrims on a common search Habits of a broad catholicity imbibed in childhood will bear their fruit in the ripeness of age

Nationalism today has grown into a dangerous virus and needs to be curbed This danger was by no means unforeseen It was looked upon as the greatest political discovery of the nineteenth century but even then a wise political thinker had the foresight to say that the task of the twentieth century would be to curb and control this spirit of nationalism Two devastating wars in one generation with the clouds of another floating on the horizon bear this out and Unesco, which has set out to plant the seeds of peace in the minds of men cannot do better than tackle this question with all the earnestness at its command It is but fair that each child should know the history of his own country and his own people, but this has been apt to be taught in such a way as to give birth to an exaggerated sense of the importance of his own country and to a distorted view of the history of other countries I believe this problem is already being tackled by Unesco Rewriting the histories of different countries is not an easy problem It might be easier to attack the evil by the writing of a history

of the world in which the achievements of different peoples and nations would be presented in a proper perspective The study of such a book in schools would tend to develop an attitude of mind which would look upon humanity as one with its different branches in the East and the West regarded as fellow families that have laboured in their own way toward human progress Needless to say such a *history* will lay less emphasis on battles and kings than on the achievements of the great of all nations in the fields of literature and art, science and philosophy, *morals* and religion

The third evil of our education today has become world wide and that is extreme specialization Knowledge has grown so vast that specialization has become inevitable for those engaged in research But it is questionable education to encourage it for the rank and file few of whom will ever aspire to be specialists and most of whom will have to bear the humdrum burdens of everyday life We are aware that industrialism has not been *an* unmixed blessing It has introduced a monotony of work which has destroyed the joy of creative activity so common among the craftsmen There must *be* some means to lessen *this* ennui of life and that something can only be supplied by a system of educat*ion* that has the whole of man before it man as craftsman rejoicing in doing man as a lover of the beautiful in painting sculpture architecture and music man as a thinker man as a social creature man as a pilgrim in search of the divine

Education has to remake the men and women of our generation The old contrast between the East and West has lost its former antithesis In addition to the superficial veneer of the Western ballrooms which now have their counterparts in India and Iran and China we find the impress of the West on the life of the teeming millions of the East The new sense of individuality the new intoxication of freedom the new zest for life the new womanhood that we have begun to see flowering in the so-called unchanging East give us a foretaste of the future in which the West and the East will be just geographical terms without the connotation of different moral political and religious attributes Democracy is an equalizer and its greatest tool is education

In this changed world philosophy too will have to change

so as not to be known as Eastern or Western The West may yet come to look kindly upon the basic Indian conceptions of *karma* and rebirth, and perhaps the scientific genius of the West may succeed in giving them a scientific basis instead of their being accepted as dogmas This may give the West a clearer perspective of the infinitude of life and a deeper insight into the mysteries of life through the psychological approach to the mysteries of Indian mysticism Similarly India too will have to learn through her contact with the virile West that life is more than a dream and something too concrete to be dealt with lightly If her new born democracy is to be a fact and not a mere political aspiration India will have to develop a new zest for life in all its richness The peace that India has preached is not a mere negation of wars but that inward peace which implies harmony in the soul and in our relations with all, be they of the East or West What we must aspire to achieve is to create a world in which man becomes conscious of the sacredness of his body as the temple of his soul and the vehicle of his mind, so that he keeps it clean and makes it beautiful and free from disease His mind has to be enriched with all the wealth of civilizations and his soul made alive to his destiny as man the spirit Only by aiming at the highest can we attain what is worth attaining though as practical men we can take only measured steps inch by inch, in the spirit so beautifully expressed by Goethe *Ohne Hast, ohne Rast*

Address delivered
at the Formal Closing Session
of the Symposium

Address
by
The Hon'ble Shri Jawaharlal Nehru
Prime Minister of India

MR President, Excellencies Ladies and Gentlemen, I am grateful to you for this opportunity of attending the closing session of this symposium I must apologize for not having attended the opening session to welcome you all here I looked forward to it greatly and it was a great disappointment that I could not do so not merely to perform a formal function of opening but rather as the President has suggested to participate in some way in your discussions and talks and to try to gather light from those discussions It is good of you to ask me to speak but I feel somewhat hesitant, because of the presence of very eminent friends who have come from distant countries, specialists and men and women of great experience and for me to say something about the great subject of your debate appears to me rather presumptuous Had I had the chance to attend some of your sessions I would have listened to what was said there perhaps sometimes participated, put a question but generally speaking listened because I would have been anxious to find out what you had in your minds and how that could help me to understand some of the problems that confront us Because most of us I suppose are burdened with the complexity of our present-day problems We live our day to-day lives and face our day to-day difficulties, but somehow that is not enough And when one seeks something behind that daily round to find out how one can solve the problems that affect the world especially one who owing to circumstances is placed in a position of great responsibility it is particularly difficult to avoid thinking about these problems During the last few weeks I have been going about this great country and seeing multitudes of human beings—my country men and countrywomen surging masses—and always a thought has come to me what is going to happen to these people what

are they thinking, in which direction are they and we—because we are in the same boat—going? And then I thought of other multitudes in other countries What about these vast masses of human beings? Here we are, some of us functioning on the political plane and presuming to decide the fate of nations, how far do our decisions affect these multitudes, do we think of them or do we live in some upper stratosphere of diplomats and politicians exchanging notes and sometimes using harsh words against each other? Politics in this context becomes rather trivial in this mighty context of the world and its vast masses of human beings and the tremendous phase of transition through which we are passing So I have no particular light to throw on the problems that you have been discussing, rather I would like to put before you some of the difficulties that I have in my mind Indeed, I hope that when I have the occasion to read some of the reports of what you have been saying to each other, perhaps they may help me to understand the methods needed to solve some of these problems

One of my chief difficulties is this that somehow it seems to me that the modern world is getting completely out of tune with what I might call the life of the mind—I am leaving out at the moment the life of the spirit Yet, the modern world is entirely the outcome of the life of the mind After all it is the human mind that has produced everything that we see and feel around us Civilization is the product of the human mind and yet strangely enough one begins to feel that the function of the mind becomes less and less in the modern world—or certainly not so much as it used to be that somehow, generally speaking mind counts for less Mind may count for a great deal in specialized domains it does and so we make great progress in these specialized domains of life But generally speaking, in life itself as a whole mind counts for less and less That is my impression Now if that is true, there is something radically wrong with the civilization we are building or have built, and which is ever changing The changes that are so rapidly taking place emphasize other aspects of life and somehow prevent the mind from functioning as it should, and as perhaps it used to do in the earlier periods of the world's history If that is true then surely it is not a good outlook for the world because the very basis on which our civilization has grown on which man has risen step by step to the great

heights on which he stands today, the very foundation of that edifice is shaken

We talk about many things, and they are important Here am I, in India, concerned about everything but more particularly about the primary necessities of life for our people I am concerned with food for our people with clothing for our people shelter and housing for our people education health etc Now these are primary necessities and of course unless you have these primary necessities it seems to me rather futile to talk about the life of the mind or the life of the spirit You cannot talk of God to a starving person you must give him food So one has to deal with these primary necessities it is true Nevertheless even in dealing with them one has some kind of an ideal or object in view which is more distant and if that ideal or objective somehow becomes less and less connected with the growth of the human mind there must be something wrong I do not know if what I say is true or if you agree with it, and I do not know even if it is true how it can improve

I am a great admirer of the achievements of modern civilization, of the growth of science of the applications of science and of technological growth Humanity has every reason to be proud of them and yet if those achievements lessened the capacity for growth in the future—and that will happen if the mind deteriorates—then surely there is something wrong about that process Because, I suppose it is obvious that the mind ultimately should dominate I am again not mentioning the spirit but that comes into the picture too If the world suffers from mental deterioration as a whole or from moral degradation, then something goes wrong at the very root of civilization or of culture And while that civilization may last a considerable time it grows less and less and ultimately it might tumble down When I look back on the past periods of history, they are very different of course but nevertheless, certain periods stand out They show great achievements of the human mind Other periods are not so One finds races achieving a high level and then apparently fading away at least fading away from the point of view of their achievements And so I wonder if something that led to the fading away of a relatively high culture is not happening today and producing an inner weakness in the modern structure of our civilization

Then the idea comes to me, what is the environment which is likely to produce the best type of human being? You talk about education and that obviously is very important But apart from the school or college education, the entire environment that surrounds us naturally affects the development of the human being What is the environment that has produced in the past these great ages of history? Do we now have that proper environment basically? Are we going towards it or away, in spite of the great progress we have made in many departments of human life? What about the industrial revolution that started about 170 or 200 years ago, and the enormous changes, largely for the good that this industrial revolution has brought about? That process, I take it is continuing and the tempo becomes faster and faster—the tempo of change Where is it leading us? It has led us in one direction—to great conflicts and possibly greater conflicts which threaten to engulf a large part of humanity in a common cataclysm

Now there is an essential contradiction in all this—this race between progress and building and the other element which destroys which is likely to destroy all that we have built up We seem to live most of us as if both were inevitable and we have to put up with it It seems to me very odd that we wish to build and build and at the same time look forward to the possible destruction of all that we build The destruction of the outer emblems of the mind and spirit may also follow Is it something I wonder some resultant of this growth of the industrial revolution that is overreaching itself? Have we lost touch with the roots that give strength to a race, to humanity or to the individual just as perhaps a city dweller loses touch with the soil and sometimes even the sun and then may live an artificial life in comfort and even in luxury There is something that he lacks something that is vital to the human being So whole races begin to live more and more an artificial life cut off from the soil and the sun Is that not so? These ideas trouble me Again I find that this growth of a mechanical civilization which obviously has brought such great triumphs and has helped the world so much, gradually affects the man and the mind The mind which produced the machine to help itself gradually becomes a slave of that machine and we become progressively as a race mechanically minded

I suppose the vitality of a group of an individual or a society is the extent to which it possesses creative imagination courage etc, but above all creative imagination If that creative imagination is lacking our growth becomes less and less, which is a sign of decay What is happening then today? Are we trying to improve in this or are we merely functioning somewhere on the surface without touching that reality which is afflicting the world, which may take shape in political conflicts, in economic warfare or in world war?

So when discussions take place on the concept of man, the Eastern ideal or the Western ideal they are very interesting to me from a historical point of view from a cultural point of view, although I have always resisted this idea of dividing the world into the Orient and the Occident I think that is a very simple way of saying something and thereby dividing our selves, by dividing into compartments like this I do not believe in such divisions I do think that there are differences, there have been differences in racial and national outlook and ideals, but to talk of East and West has little meaning The West, the modern West—meaning thereby a great part of Europe and the Americas—has developed a certain type of civilization more especially during the last 200 years or so based no doubt on certain basic traditions derived from Greece or Rome But it is the tremendous industrial growth of which I have spoken that has made the West what it is the scientific industrial growth I can see the difference between the industrialist country and the non industrialist country I think the difference say between India and Europe in the Middle Ages would not have been very great just as there are differences between any of the great countries of Asia I feel the East West division is a misleading approach which prevents us from thinking correctly and that differences have crept in or have been intensified by the process of industrialization mechanization, etc. which has promoted material well being tremendously and which has been a blessing to humanity But it is somehow if not in the past now perhaps corroding that life of the mind and thereby encouraging a process of self destruction I am not for the moment talking or thinking about wars and the like We have seen in history races come up and gradually fade away in Asia in Europe and other places Are we witnessing any such thing?

It may be that this will not take effect in our lifetime In the past there was at least one great consolation—things happened in one particular quarter of the world If there was a collapse in one part of the world, the other part carried on Now the whole world hangs together in life or in death, so that if this civilization fades away or collapses it takes practically the whole world with it There is no part of it left, in a sense to survive as in the olden times it did During the so called dark ages of Europe there were bright periods in Asia, in China, in India, in the Middle East or elsewhere So that, in the old days if progress was limited, disaster was also limited both in extent and intensity Today when we have arrived at a period of great progress we have also arrived at a period of great disaster, and it is a little difficult for us to choose some middle way so as to assure a little progress and possibly limit the risks of disaster Can we avoid that disaster? That becomes the major question and idealistic conceptions of the concept of man, etc become rather academic although they are very important At any rate, for one who has to carry a burden of responsibility, the practical aspects of this question are a great cause for anxiety So I should have liked your Conference to throw light on this question Am I right in saying that the mental life of the world is in a process of deterioration chiefly because the environment that has been created by this development of the industrial revolution does not give time to individuals to think, does not give them that opportunity? There are many great thinkers today I do not deny it, but it is quite likely that they might be submerged in the mass of unthinking humanity

Again we are dealing with and talking a great deal about democracy and I have little doubt that democracy is the best method that I can see of all the various methods available to us for the governance of human beings At the same time we are seeing today—by today I mean the last decade or two decades—the emergence of democracy on a mass scale and in a somewhat uncontrolled way When we think of democracy we normally think of it in the rather limited phases of the nineteenth century or the early twentieth century Now something has happened since then owing to this remarkable technological growth and meanwhile democracy has also spread in the form of adult suffrage and similar measures with the result

that we have vast masses of human beings brought up by this industrial revolution not encouraged or given opportunity to think much, living a life which from the point of view of physical comfort is ever so much better than in any previous generation, but seldom thinking or seldom having a chance to think And yet at the same time it is the vast mass of human beings that will, in a democratic system ultimately govern or elect those who govern

Are they likely to elect the right sort of persons they need, or more or less right persons? That becomes a little doubtful And I think it may be said without offence—and I certainly can say it without offence for I belong to the tribe of politicians—that the quality of men who are selected by this modern democratic method of adult suffrage gradually deteriorates There are outstanding individuals chosen no doubt but it does deteriorate because of this gradual lack of thinking and the application of modern methods of propaganda All the noise and din and the machinery of advertisement prevent man from thinking He reacts to this din and noise and he produces a dictator or a dumb politician one who is insensitive who can stand all the din and noise in the world and remain standing on his two feet gets elected the other man collapses because he cannot stand all this din It is an extraordinary state of affairs It is all very well for us to praise the growth of democracy but the point I wish to make is not in regard to democracy but rather to the fact that modern life—I go back to what I said at the beginning—does not encourage the life of the mind If it is so, that is, if the life of the mind is not encouraged then inevitably—it follows for me—civilization deteriorates the race deteriorates and ultimately either collapses in some great cataclysm or simply fades away and becomes as other races have become So I would like the eminent delegates of this Conference who have come here to help me to find some answer to these doubts and difficulties which arise in my mind—and I suppose they are not only in my mind but also in the minds of large numbers of people elsewhere

Appendixes

Appendix I

Basic Document drawn up by the Unesco Secretariat on the basis of suggestions received from Professor Olivier Lacombe and Swami Siddheswarananda
Proposed Theme for Discussion The concept of man and the philosophy of education in East and West

THE GENERAL PROBLEM EAST AND WEST

East and West can each preserve its own peculiar genius without becoming encased in a sterile hostility It has often been rightly said that for the one party to view itself in contrast with a distorted and over-simplified conception of the other is to run the risk of losing all but the most superficial of its own values it is also to run the risk of stagnation in a tradition doomed to degenerate for lack of revitalizing contact with the outer world This is the reason for the many meetings discussions symposia investigations and visits that have taken place since the beginning of the present century with the object of developing a better understanding between the parties

Unesco could not remain indifferent to this problem it was bound to face it squarely in the present circumstances of the world brought about by the increasingly rapid process of unification the reduction of distances the growing importance of technology the gradual attainment by all the peoples of political independence and international responsibility and above all the disquiet and perplexity prevailing among the *two* great civilizations of yesterday ready to give birth to the *one* civilization of tomorrow but cowering under the threat of a world crisis far beyond their capacity to control

It was Unesco s task to help each of these two civilizations to view itself in just relation to the other and to help both of them to adopt a policy with regard to the grave problems that now beset all nations problems demanding a reassessment of their traditional wisdom in order that man may develop all the potentialities of his

kind in an environment which he has created but which he is not yet able to dominate by the power of the spirit If peace is to be soundly based the old intercourse between East and West must be revived and efforts must be made with all possible speed to bring about mutual understanding between them in preparation for that future civilization which should be the common property of all men at the same time as the expression of their unity and of the ideal they live to serve

Those are the reasons for organizing this discussion between thinkers and philosophers with the help of the Indian Government and National Commission Such a discussion conducted in the atmosphere of candour and impartiality proper to philosophical contemplation should serve as a leaven to produce a better understanding between the peoples

OBJECT AND METHOD OF THE DISCUSSION THE DISCOVERY OF PRACTICAL CONVERGENCIES

What object and what method can be proposed for such a discussion? The first snare to be avoided would be that of suggesting any attempt to secure an artificial uniformity or a surface deep reconciliation The alternative danger would be that of dissipating effort in academic discussions with little prospect of leading to agreement

To avoid both these dangers the discussion organized by Unesco should derive from the ideas set forth by Mr Jacques Maritain at the Second Session of Unesco s General Conference and represent *an effort to discover practical points of convergency in the light of the fullest possible mutual understanding* This should not however in any way debar each philosopher from explaining his own doctrinal attitude

THE SELECTION OF A TOPIC FOR DISCUSSION

In order to find a common ground for the conduct of discussion it was felt necessary to suggest a specific topic so as to avoid the mere accumulation of unco-ordinated ideas on the other hand it was desirable that the proposed topic should be capable of epitomizing every significant aspect of the civilizations represented It is in the attempt to satisfy these two requirements that Unesco has chosen as the subject "*The Concept of Man and the Philosophy of Education in East and West*"

The problems of the philosophy of education in its relation to the concept—or concepts—of man in each civilization do in fact help to bring out the fundamental conceptions of man in his relationship

to the divine principle to the world nature, society and the practical sphere of action historically and in the contemporary world They involve comparison of the various forms in which spiritual and ethical ideals take shape with the more immediate question of organization and practical value in societies in which technology is necessarily taking an ever growing place they thus permit consideration of the different ways in which ideals can be implemented in the actual circumstances decreed for us by history and of the ways in which each civilization may attain to under standing of others through the knowledge of their methods of dealing with the problems arising out of the contemporary develop ment of societies

This discussion might thus lead on finally to the following ques tion *What are the elements in each civilization conducive to the definition of the cultural and philosophic bases of a well balanced education adapted to the spiritual and material needs of contemporary man and apt to promote understanding between the peoples respect for human rights and peace?*

The feature distinguishing the discussion organized by Unesco from the many similar efforts made in the last 50 years would be precisely this attempt at a re definition of the values of civilization not so much in themselves as in their practical implications in their significance in relation to one another and as a body in relation to the contemporary problems of mankind

THE CONCEPTS OF MAN IN EAST AND WEST TRADITIONAL CONTRAST BETWEEN THEM

When we consider the individual concepts of man in what form do we find the contrast between East and West to be usually expressed? We may summarize briefly the traditional formulations of these concepts even if such formulations by their over simplicity do not appear to present a faithful picture of the reality

Firstly certain characteristics of Western man have appeared most likely to place him in opposition to Eastern man and indeed have been held to express the essence of Western civilization The West emphasizes the distinction between the ego and the non ego regarding nature as man s domain and as an instrument at his service This accounts for the development of a form of thought which is most characteristically expressed in science making use of discursive reason and distinguishing one object from another by analysis it accounts equally for the importance attributed to the self and to self interest the striving after individual originality the insistence on freedom directed towards personal welfare and the exercise of power and the need for regulating these freedoms

and personal desires by means of social institutions Western man, it has been said by nature looks out upon the world with the desire to dominate it he is not naturally inclined to meditation the technical therefore tends to take precedence over the spiritual rational analysis over intuitive communion and the exercise of the intellect over metaphysical experience The sharp separation between the sacred and the profane leaves to reason and science the responsibility of ordering daily life for the common good regarded as the sum of individual interests Western man it is said again does not generally aspire to escape from the bounds of the temporal to eternity he believes in progress rather than tradition and is ever in search of new ideas inventions and fresh discoveries All this results in a form of thought a way of life and action in which technology founded on science plays a major part the mastery of material things opens up tremendous vistas and the practice of government has led to certain fine achievements But Eastern man is struck at once by the instability of Western values and the inability of Western men to give those values the predominant place in the direction of human development in his view Western civilization is unable by itself to give man tranquillity essential contentment and roots in the world

The East appears to sum up the whole sense of its civilization in the key word spirituality In most of the civilizations at least those which may be described as oriental (and here many fine distinctions must be made) Eastern man seeks first and foremost to find his place in and to develop more fully his close communion with nature instead of subduing it by technical skill or forceful intervention Hence in contrast to the discursive science of the West the development of forms of spirituality laying emphasis upon the intuitive experience of a profound unity of being or on daily contact with the sacred regarding all things as the manifestation of a fundamental reality which could only be distorted by analysis or of a divinity by whose laws the whole world of man and nature is governed hence too the idea of the essential bond between all individuals in a single spiritual universe and the striving after spiritual elevation in which the mundane world is abandoned and the way opened to higher forms of existence Eastern man it is said is therefore naturally given to introversion he seeks his real being by the repudiation of the apparent self cheerfully despising the material goods of this world To him the sacred essence is every where and the profane cannot survive save imbued with it Development is but an illusion and the true life is situated in eternity The sage s mind is more concerned with meditation on and the ever fuller experience of a tradition than with the search for new discoveries or formulae All this results in a form of thought a way

of life and action in which harmony with nature and communion with the divine founded on spiritual contemplation play a major part, and in which the examples of sanctity and wisdom are often achieved in societies which sometimes on the contrary give little thought to the improvement of living conditions for the mass of the people But Western man for his part is prone to see the factors of possible stagnation in the tradition of the East the sterility of its resignation the undemonstrability and incommunicability of its metaphysical intuition Eastern civilization in his view is incapable by itself of extending the benefits of progress, culture and even spirituality to the race of men as a whole

THE ERROR OF SIMPLIFICATION

The foregoing gives in brief the general picture of the opposition between East and West as traditionally presented It can hardly be denied that there is some truth in it particularly when the most obvious outward features of these two forms of civilization are considered

If these contrasts are carried to extremes however we should be led to the conclusion that the Eastern outlook and the Western outlook are the exact complements of one another but lack the minimum points of identity which would enable them to benefit from what each can teach the other In this light the ideal of man as man in the fullest sense would remain permanently beyond the scope of either side with no hope of its attainment for lack of mutual understanding

Many years ago however the idea was evolved that it is wrong to simplify and sharpen that opposition in this way Firstly each of the two civilizations contains so many diverse elements that it cannot be permissible to reduce either to a simple homogeneous formula Eastern man too takes steps to order earthly life and to transform nature to him science is indebted for certain intellectual discoveries particularly in mathematics and astronomy without which analytical reason could never have forged ahead and ultimately mastered the material world he is responsible for some of the technical discoveries on which the life of mankind rests and the history of the nations of Asia shows too what a high pitch has been reached at certain periods in the art of organizing societies for the common good and for the free development of the individual

The West for its part has also produced saints and sages whose teachings are still a living influence it has seen and still sees philosophical and spiritual movements of a high order, mystical communion an intuitive sense of the unity of being the desire for

eternity universal love renunciation are all essential parts of its tradition Its very science and the derivative technology are the fruits of primarily disinterested research in which a remarkably fine aspect of intellectual power has come to flower The West has discovered and adopted humane values of the very highest importance freedom of thought the universal application of law and the dignity of the individual are the cornerstones of Western humanism and in Christianity itself, the Franciscan tradition extends to the whole of nature the charity that expresses the link between every created thing and God

Secondly it is impossible to speak of *the* civilization of the East or *the* civilization of the West both terms cover groups of civilizations *differing profoundly from one another* Can we for instance, confound the culture of the Latin and the Slav worlds? Are there not in Asia religions recognizing no personal God side by side with essentially theistic creeds? Can we fail to distinguish between the traditionally negative attitude of the Hindus towards the State and the art of government practised for centuries by the Chinese? Does the term oriental mean the same thing when applied to the Islamic and the Buddhist civilization?

History shows us that each of these cultures is the product of the intermingling of different streams in the West the Mediterranean contribution is faced by that of the barbarian invasions in Asia the agricultural societies of the great river valleys by the successive influxes of nomadic peoples Here we see a striking parallel There are equally striking parallels in the alternation of wars and cultural revivals Nay more Asia has to a large extent made Europe what it is even though it can no longer recognize itself in what Europe has become Long before the East had to define its attitude towards all that Western expansion offered or imposed upon it the West—whose religion incidentally was derived from the East—first became aware of its identity in the Middle Ages in contradistinction to the East whence invasion threatened even while Oriental learning wisdom and the refinements of Eastern civilization exercised their lure The Arabs penetrated far into France and settled in Spain Mongols imposed their law upon a great part of the Slav world and the Turks lay for a long while at the gates of Vienna On the other hand the Crusades established Christian dominions in the heart of the Middle East It is also significant that Arab civilization for example contributed to Europe not only a conception of love which brought about a renewal of social relations and literary inspiration but also a wisdom and a philosophy directly derived from the main currents of Greek thought Accordingly the first attempt at a synthesis recorded by Western civilization in the Middle Ages namely the research for a means of reconciling

ancient philosophy and Christian dogma was made possible by the flowering of Arab philosophy itself the heir to Mediterranean thought Speaking generally the great Renaissances forming land marks in the history of European and Asiatic civilizations were the results of some sudden eruption from abroad Buddhism, for instance whose birthplace was India took firmest roots in other Asiatic lands

It would seem therefore today that it should be easy to find common ground and that a revival of civilization should be at hand as the fruit of increased and close exchanges Men owing allegiance to different traditions can meet and understand each other in many matters the common po session of reason makes converse and the comparison of ideas possible the similarity of the ethical principles of the great religions bespeaks an everywhere similar aspiration towards spirituality the mentality of our primi tive forefathers underlying that of civilized men peoples their world with myths in which we find profound analogies the material needs of life, the common necessity of food shelter and clothing the experience of human labour in the midst of nature the use of the same technical methods represent the *de facto* unity of the world mutual understanding and respect for one another s culture and the knowledge of their contacts in the course of history, make it possible for the peoples to live side by side in fruitful intercourse lastly the necessity of living peacefully in a closely knit world whose component parts have become intimately interdependent now compels all men to reach agreement on a form of organization and balanced system in which all peoples and all civilizations can take their place

HISTORICAL ORIGINS OF THE DISCORD

An inward understanding between the civilizations of the East and the West seems therefore feasible if we study each of them in itself and in all its complexity But it is not enough to clear up a simple mutual misunderstanding it is also necessary to remove a more grievous confusion born of the experience of contemporary history and of contacts which that history has witnessed

In the last few centuries Western science and technology have been carried to every country in the world not only by their own force of attraction but by virtue of the power they have conferred on those commanding them It is therefore not surprising that to the Eastern peoples the West has appeared to be solely concerned with technical matters using analytical reason alone as the servant of interest wholly taken up with material things and incapable

of any higher aspiration Nor is it surprising that the agents of this expansion sometimes conducted by force, found the East impenetrable and saw in it as it withdrew into itself, only a picture of stagnation and poverty

Hence the tragedy in the relations between the two civilizations hence the difficulty in finding a sphere for better understanding between cultures so prejudiced against each other

Seeing this we see the full significance of the discussion organized by Unesco it is the frank recognition of this very tension which may bring together Eastern and Western man provided that both are made aware of the situation and the needs they now have each alike to face

THE UNIVERSALITY OF HUMAN PROBLEMS AND MAN S ASPIRATIONS IN THE PRESENT DAY WORLD

It is by assimilating Western technical advances that the peoples of the East are now achieving full political independence and responsibility for the conduct of their own affairs in the same way they can raise the living standards of growing populations now a prey at every turn to epidemics famines and natural calamities as Swami Siddheswarananda writes The intimate relations between economic conditions and cultural standards have to be examined When millions and millions in the East have nothing to eat to speak of humanism and the evolution of the concept of man is just a caricature Efficient steps have to be taken to liquidate illiteracy and hunger and illness Whatever the spiritual traditions of a people it would be impossible today to neglect the technical achievements which alone can enable men to survive in a world that those achievements have transformed The assimilation of this technological knowledge means for the East the undertaking of an enormous programme of political and social organization educational development modernization of agriculture and industrialization What forms and what new significances will its spiritual traditions assume in this new context? They have a greater part than ever to play and that part may well be vital to keep man in mind of what is loftiest in himself and what might be in danger of extinction The East is therefore seeking a redefinition of its wisdom an assessment of what is most vital in its content it is also anxious to assimilate the traditions of the Western mind which has for a long time been associated with the teachings of science and incorporates in its wisdom the lesson of nature transformed by human labour The East is therefore trying to eradicate from its tradition any factors too slavishly associated with the past sub-

stituting a creative tradition renewing its content by contact with reality and courting encounter with other civilizations *In short the East desires to evolve a form of civilization in which both the material needs and the spiritual aspirations of man may find satisfaction*[1]

As for Western man he can now less than ever be content with the mere technical achievements due to the progress of science or by a system of ethics based on interest or ambition Man has been outstripped by the power of the instruments he has himself created which have so transformed the world and have given rise to such new and complex problems that the generally (and often implicitly) accepted values thus suddenly challenged are no longer sufficient to teach men how they should use their power and organize their relationships for the peace and happiness of the world Even the freedom of science is threatened by governmental controls The dangers which the lust of power may hold for the survival of man kind are only too obvious How far can man s wish to adapt his surroundings be allowed to go? How can men be inspired to use the resources at their disposal for truly humane purposes? *The West is seeking to rediscover in its ethical and political tradition ideals* capable of adaptation to the present circumstances of the world and of serving as a guide to mankind in the crisis through which it is passing But it may also derive new suggestions from the wis dom of the East calculated to provide a counterpoise to its own scientific and technical tradition

Is a synthesis possible? Can a comparison of the concepts of man characteristic of the East and West help to disclose values on which a humanism adapted to our times may be based? The Unesco discussion will be called upon to go deeply into this question Put briefly the technical and material needs common to all the nations and the urgent demand for a statement of values on which they can all agree while preserving their own characteristic features provide the common ground on which it is possible to engage this discussion

EDUCATION—THE CRUX OF THE MATTER

In both East and West, education is today the crux of the problem the training of technicians to play an efficient part in society the education of every individual without any form of discrimination

[1] This has been admirably expressed by Rabindranath Tagore in speech delivered to his compatriots Let me make it clear that I am not distrustful of any civilization because it is foreign. On the contrary I believe that encounter with such forces is necessary to preserve the vitality of our intellectual nature European culture has come to us with its speed as well

to fit him to develop his potentialities to the full and to play his part as a free man and lastly the education of man in general so that he may learn to control his own discoveries and may at last attain to wisdom The object of education should thus be to form men and women in every civilization capable by allegiance to their values and knowing how to define them anew, of preserving their humanity in the daily stress of life from the constant dangers created by the growth of new factors in the conditions of society

Placed thus in relation to the ideal of man which each civilization has inherited from its past and which it is seeking to define anew in the light of modern needs educational problems are seen in their full significance and scope How can men be educated today in the different cultural communities to adapt them for living in the modern world to help them to raise their standard of life to attain to greater nobility and to retain their cultural originality to help each nation to understand the others and lastly to aid in the establishment of human rights and of justice and peace?

There have been many educational experiments in both East and West connected with the transformations which the ideal concept of man has undergone in the last few decades in India the impetus imparted by Rabindranath Tagore and by Mahatma Gandhi in the Islamic world and in many other parts of the East the present campaigns for the extension of education and its organization on a democratic basis in the West the movements initiated by Mrs Montessori John Dewey and Jean Piaget and the new education experiments calling into play the creative freedom of the individual and the fruits of practical experience and lastly the immense amount of work being done everywhere for the training of executives and technicians Elementary education technical training and general education designed to produce the fully developed men and women of tomorrow are thus indissolubly linked But it may well be impossible to combine all these movements effectively, unless the present efforts of civilization can produce new ideals The discussion which Unesco is organizing will have fulfilled its purpose if it helps towards the definition of those ideals

ADDENDUM SOME CRUCIAL QUESTIONS

We have deliberately refrained in the foregoing from too precise a definition of specific questions which might confine the discussions

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as it knowledge Although w[illegible] have ass[illegible]ted it [illegible]nly imperfectly [illegible] it h[illegible] [illegible] has roused ou[illegible] [illegible] from the inertia of [illegible] [illegible] [illegible]warenes, resul[illegible] from the [illegible] contrast [illegible] [illegible] ou[illegible] [illegible] traditions

within unduly narrow limits militating against their successful development and effect We have tried simply to describe the premises of the problem facing the whole of mankind Nevertheless without pretending to set forth successive headings for the discussion, we may list some of the standpoints from which the civilizations of the East and West have defined their ideals of humanity and which may today give us a clearer picture of the terms in which man is in general questioning his own nature We have attempted as an example to give below a list of such aspects of the problem in the hope that they may suggest instances which will facilitate the clear statement of the questions involved and orderly reflection upon them

Man in relation to the divine and the sacred Relationship between the sacred and the profane relationship between religion and spiritual ethical and political life [1] The claims of a life transcending everyday worldly existence The concept of perfection immanent in human nature and that of original sin or the fall of man and their consequences to the philosophy of education [2]

Man in relation to the cosmos and nature The concept of man mastering nature by technology, and the concept of man in communion with nature The attitude of man towards the animal kingdom [3] The cosmic significance of non violence The idea of universal justice [4]

Man and knowledge The value of knowledge as a means of man s salvation and betterment Initiation and discovery Knowledge and wisdom the limitations to be assigned to the power of the intellect intellectual learning and the cultivation of the whole being [5] Relation between instruction and education The traditional ideals of education viewed in regard to the need for the universal dissemination of knowledge

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1 P l is whi h will come to mind re h m h nc f he Sharia or Kor ic Law as syn thesis of r tual law hics and social org iz on the rela ions be wee the three degrees of morality in India the lofty moral y of the sage he mor l y of special du ies arising w h social sta us (svadh rm) nd las l gene l hich impos g blig t ons in regard t all h man be gs (sam yadh rma) t

2 "The Ind view of l f asserts h perfection is lre ly in man nd that the func ion of educ t on is only discove (Swam S hiþere Ananda)

3 A compariso ma be mad between the respect for usual life found in certai Eastern civilizations and the Western movement for the preve ion of cruel y to animal ogether wi h the measures t ken in he West for the preserv ion of i ral be les and wild lif On he othe hand conside n may be given the possibl d ngers, from man s poin of view of too ques ioning respect for e.

4 Instances which w ll come to mind re he idea of immanent justice in the West the law of Karma in H nd ism nd in Bud hism and the oncept of d ine justice in Islam

5 A example oft n quoted is he of Chinese thought, which is directed less towards purely i tellec ual development than w rds he cul ion of the whole man. It is also s d that Western peoples are more int rested in objec ve judgments, while Eastern peoples are more concerned wi h lue judgments.

Man and ideals The influence of ideals in relation to conduct and institutions Relation between expediency and virtue The importance of aesthetic values in education their relation to ethical values the concept of the cultivated man Relation between an ideal commensurate with man and the claims of a form of life transcending the purely human [1]

The individual and society The humanistic bases of democracy purely political democracy and social and economic democracy, the importance of these concepts in establishing the relations between the individual and the community The ideal of justice and the fact of inequality [2] The conceptions of education and the ideal of equality the participation of all in cultural life The betterment of the individual and social harmony [3] Education as a means of liberating the individual and education as a means of fitting him to a cultural community The ideal of conformity and the ideal of individual development.

The part played by political institutions and their significance What part can national and international political institutions play in the formation of a new humanism?[4] The problem of the relationship between ethics and politics [5] The value of patriotism and the dangers of nationalism

Man and his neighbour The problem of tolerance its meaning tolerance and scepticism The importance of altruism

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[1] Consideration may be given to the significance of Nietzsche's philosophy, that of the practice of Yoga and the importance in Indian civilization of philosophy such as that of Aurobindo.

[2] In the various cultures should the status of the individual be regarded as implying strict equality or may it include inequality with respect to function or other considerations? Comparison may be made between the Western distinction between commutative and distributive justice, the Islamic conception of the equality of all believers before God and the hierarchical principle in traditional Hindu society which is nevertheless bound up with the law of Karma applying equally to all.

[3] The wisdom of the Chinese sages Mencius and Confucius, for example, consists largely in the attempt to reconcile these two terms; comparison may be made with certain theories of democracy in the West and the East.
Comparison may be made between the Hellenic and the Chinese traditions regarding government as an exercise of reason and virtue, the traditional dissociation of social and political matters in Hinduism and the application of the Koranic Law to the exercise of power in Islam.

[5] It would be easy to discover in all civilizations the self-same temptation to reduce politics to a question of technique entirely divorced from ethics; we may also see a series of similar reactions against this tendency: e.g. Plato and Aristotle in Greece, medieval Christianity regarding government as the application of political virtue, the dual concept of dharmasastra regarding politics from the moral standpoint and arthasastra regarding it from the technical aspect in India, the idea of civilization as higher than the idea of the State in Confucius and, in all Chinese wisdom, the concept of the ordering of life and human activities, including but transcending politics, with the object of achieving the integration of society in a cosmic system.

Man in relation to time and history Time and eternity Progress and survival The concept of tradition and the concept of renewal as formative factors in the philosophy of education

The significance and scope of action The relationship between action and contemplation the sage the philosopher the saint and the mystic, and their reactions to the claims of activity The ethical and political significance of non violence is it to be regarded as an ultimate end of human progress or as a current means?

Man his physical condition and his work The traditions proper to different cultures in relation to the technical knowledge of the world and the requirements of the ordering of life The overcoming of the self and the overcoming of external conditions the relationship between the ascetic ideal and the desire for greater welfare The importance of the philosophy of human labour

Man s position in present world conditions Spiritual tradition and material development The influence of scientific advances on the concept of man considered from the standpoints mentioned above Man s attitude to what is different and what is new other ideas other communities new methods The problem of comprehension and assimilation Man as a member of a community and as a citizen of the world means of introducing the view of the world as a whole into education

Contemporary problems and experiments in education In the light of certain major experiments of recent times the following problems may be posed in an instructive form Tradition in education and changes in the social structure Education and instruction The education of the full human being and the training of the specialist The education of the individual as such and the training of socially useful citizens The ideal of conformity and the ideal of individual development in education The importance of manual work and craftsmanship The importance of the arts and aesthetic experience The part played by the teacher as a guide in initiation compared with that of the teaching profession as a social institution Experiments in "modern education" the appeal to free initiative and practical experience Education in relation to the problem of a world conscience

CONCLUSION

Possible definition of what constitutes a well balanced democratic education inspired by ideals satisfying the requirements of our time,

Appendix II

BIO BIBLIOGRAPHICAL INDEX OF AUTHORS

ALBERT BÉGUIN

Born Switzerland Canton of Neuchâtel on 17 July 1901 studied at Geneva University and later at the Sorbonne

Taught French literature and the language and literature of classical Greece at the University of Halle Wittemberg (Germany), in Geneva and then at Basle University from 1929 to 1945 Since 1945 has been living and writing in Paris

In 1941 Albert Béguin founded the review *Cahiers du Rhône* later becoming its editor and publishing the works of the French Resistance writers On the death of Emmanuel Mounier in 1950 took over the editorship of the monthly review *Esprit* The late Georges Bernanos appointed him his literary executor

Béguin s works include *L Ame romantique et le rêve Essai sur le romantisme allemand et la poésie française* (1937 new revised edition 1945) *Gérard de Nerval* (1937 new revised edition 1946) *La prière de Péguy* (1942) *L Eve de Peguy* (1948) *Leon Bloy l impatient* (1943) *Léon Bloy mystique de la douleur* (1948) *Faiblesse de l'Allemagne* (1945) *Balzac visionnaire* (1946) *Patience de Ramuz* (1949) *Blaise Pascal* (1952)

He is joint author of the following works *Hommage à Bergson* (1941) *Léon Bloy* (1943) *Georges Bernanos* (1948) *Le romantisme allemand* (1937 and 1947) *Cinquante ans de decouvertes* (1950)

Has translated from German works by Goethe Tieck Arnim Hoffmann Mörike Jean Paul Richter (10 volumes published between 1929 and 1950) has edited or adapted works by St Bernard de Clairvaux (*La Queste du Graal*) Maurice Scève Pascal Gérard de Nerval Balzac (complete works) and Léon Bloy and has contributed to *Esprit Fontaine Les cahiers du sud La nef Poésie 46 Revue de Paris Revue d histoire litteraire Etudes carmélitaines Une semaine dans le monde Terre des hommes Temoignage chrétien Gazette de Lausanne La table ronde Wort und Wahrheit* etc

JOHN TRAILL CHRISTIE

Born October 1899 scholar of Winchester College 1918 he re ceived a commission in the Coldstream Guards and later won a scholarship to Trinity College Oxford

Was appointed Senior Classics Master at Rugby School then Fellow and Classical Tutor of Magdalen College. After successively occupying the post of Head Master at Repton and Westminster became Principal of Jesus College Oxford in 1950

Has published articles, reviews and addresses on religious and educational subjects

RAS VIHARY DAS

Born about 1894 in a village in the district of Sylhet now part of Eastern Pakistan Won scholarships to a middle vernacular school then to an English secondary school and finally to Calcutta University While yet a student he helped to organize a night school and founded a society to help needy students

For his M A degree he studied dialectical and metaphysical logic with special reference to Hegel s *Logic* Kant s *Critique of Pure Reason* Fichte s *Science of Knowledge* and Lotze s *Metaphysics*

In 1946 received an appointment at Calcutta University and in 1951 became Dean of the Faculty of Philosophy at Saugar University

His first published book *The Self and the Ideal*, was an essay in metaphysical construction based on moral consciousness Two of his works the *Essentials of Advaitism* and *Ajnana or the Theory of Ignorance* (written in collaboration with two friends) provide an account and criticism of the *Advaita Vedanta* In English he has also written *The Philosophy of Whitehead* and *A Handbook to Kant s Critique of Pure Reason* and in Bengali a general work on Kant *Kanter Darshan*

CLARENCE H FAUST

Born 11 March 1901 at Defiance (Iowa) Was elected President of the Fund for the Advancement of Education on 4 April 1951 when the Fund was created by the Ford Foundation as a non profit making corporation to co-operate with primary secondary and higher educational establishments for the improvement of education

Before accepting this appointment had since 1947 been on the

staff of Stanford University, first as Director of the Libraries then as Dean of the Faculty of Humanities and Sciences In 1949 he was Acting President of the University

He was formerly on the staff of the University of Chicago where he held various posts over a period of 17 years Dean of Students in the Division of Humanities Professor of English and Humanities and Dean of the Graduate Library School

Clarence Faust is a graduate of Chicago University the North Central College and the Evangelical Theological Seminary

His publications include *Jonathan Edwards* (in collaboration with Clarence Johnson 1935) *Jonathan Edwards and Science* (American Literature 1930) *The Background of the Unitarian Opposition to Transcendentalism* (Modern Philology 1938) *Emerson's Literary Theory and Practice* (Modern Philology 1946) *From Edwards to Emerson* (the Colver Lectures delivered at Brown University in 1945) He is also a contributor to *General Education in Transition—A Look Ahead* (1951)

HELMUTH VON GLASENAPP

Born 6 September 1891 in Berlin studied at the Universities of Tuebingen Berlin Munich and Bonn and since 1918 has been lecturing on Indian civilization and comparative religions in the first three of these as well as at Koenigsberg University Is a Professor at the University of Tuebingen and a member of the Mainz Academy of Science and Literature the Academy of Indian Civilization in Lahore (now Nagpur) and the All India Sanskrit Parishad

In 1927 28 he visited India and in 1931 and 1938 travelled extensively in Europe Japan China Indo-China Indonesia North and South Africa North and South America the Fiji Islands and Australia primarily in order to study at first hand the influence of Indian civilization and immigration

He is the author of numerous books and articles (in German) on Hinduism Jainism Buddhism Indian literature and philosophy notably on the Indian philosophers Madhva Vallabha and Shankara and also the two following works *Kant and the Religions of the East* and *The Five Great Religions* The following of his works have been translated *Jaina Dharma* (translated into Gujrati 1927) *Brahma and Buddha* (French translation 1937) *The Doctrine of Karma in Jain Philosophy* (English translation 1942) *Buddhist Mysteries* (French translation 1944), *Indian Philosophy* (French translation 1951)

HUMAYUN KABIR

Born Faridpur Bengal, in 1906 Humayun Kabir has been a professor at both Andhra and Calcutta Universities His two main interests have been philosophy and poetry on the one hand and politics and administration on the other Was Secretary General of the Bengal Peasants Party and its leader in the Bengal Legislative Council Was appointed Chairman of the Ethics and Politics Section of the Indian Philosophical Congress in 1941 and 1945 and of the History of Philosophy Section at the Silver Jubilee Session of this Congress in 1950

Was Deputy Leader of the Indian delegation to the Third Session of Unesco s General Conference Now Adviser on Education to the Government of India

His English writings comprise *Mahatma and Other Poems* *Our Heritage* (a survey of Indian history) *Poetry Monads and Society* (a study in aesthetics) *Men and Rivers* (a novel translated into Swedish)

A contributor to the volume *Contemporary Indian Philosophy* and acts as Secretary to the Board of Editors for *History of Philosophy Eastern and Western*

Made the first English translation of Kant s Introduction to the *Critique of Judgement* and has published many works in Bengali among them *Immanuel Kant* *Marxvad* etc

YENSHO KANAKURA

Born 17 November 1896 graduate of Tokyo University Assistant Professor at the Imperial University of Tohoku Sendai later Professor of Indian civilization in the Faculty of Law and Literature then Dean of the Faculty of Literature and since 1949 Dean of the Faculty of General Education

Between 1923 and 1926 visited England Germany and India to pursue his study of Indian civilization From 1949 has been a member of the Japanese Science Council

His chief works are *An Enquiry into the Veda Philosophy* *Indian Moral History in Ancient Times* *Indian Moral History in Medieval Times* *Formation of Indian Spiritual Culture* *An Introduction to Indian Philosophy* *Indian Thought and Culture* *Sanron Gengi* *Indian Studies by Japanese* *Study of Dharma* and many other works on Oriental philosophy

IBRAHIM MADKOUR

Born 1902 student at the Teachers' Training College, Cairo and then in France, where he graduated in literature and law and later obtained a D Litt Professor at the Fuad I University Cairo 1935 to 1940 Elected to the Egyptian Senate, and since 1945 has been a member of the Fuad I Academy of Arabic

Among his French writings are the following *La place d Al Farabi dans l école philosophique musulmane* (Paris, 1934) *L Organon d Aristote dans le monde arabe* (Paris, 1934) *La réforme agraire* (Revue de l Egypte contemporaine) *Le canal de Suez et l economie égyp tienne* (Revue de la Société des études belges) *Ibn Sina et l alchimie arabe*

In Arabic he has written *Lessons of the History of Philosophy* (Cairo 1937) *Muslim Philosophy a system and its application* (Cairo 1947) *The Governmental System in Egypt* (Cairo 1937) *Al Chifa (Healing) a General Introduction to the Philosophy of Ibn Sina (Avicenna)* (Cairo 1951)

While continuing to lecture in the Faculty of Literature Ibrahim Madkour has for the past 10 years been Secretary of the Senate Finance Committee

He is particularly interested in the history of Islamic thought and in social science Since he became a Member of the Academy he has also taken a keen interest in the problem of the Arabic technical vocabulary which needs to be improved and amplified to meet the demands of modern scientific instruction

GUNAPALA PIYASONA MALALASEKERA

At the age of 52 Gunapala Piyasona Malalasekera Ph D is Dean of the Faculty of Oriental Studies and Professor and Head of the Department of Pali (in which is included Buddhist Civilization) at the University of Ceylon He is President of the World Fellow ship of Buddhists (with representatives from 53 countries) Presi dent of the All Ceylon Buddhist Congress to which are affiliated Buddhist religious cultural and humanitarian societies in Ceylon member of the Council of the Royal Asiatic Society (Ceylon Branch) Honorary Secretary Ceylon Society of Arts (since 1927) member of the Advisory Board of the National Museums of Ceylon and of the Archaeological Survey of Ceylon member of the Exe cutive Committee of the Singhalese National Council for Unesco

He has travelled very widely in Asia America and Europe and has just returned from an extensive tour of South East Asia including Burma Thailand Singapore Malaya Cambodia Viet Nam

Laos and India during which he lectured on Buddhist culture

He has taken part in numerous international conferences both cultural and religious including the Wembley Conference of Living Religions (1924), the Inaugural Conference of the World Fellowship of Faiths (1936) the East West Philosophers Conference in Hawaii (1949) and the All India Oriental Conference (October 1951) where he presided over the section on Pali and Buddhism He broadcasts regularly on cultural subjects over the Ceylon radio and has given a number of broadcast talks in India England and America

His published works include *The Pali Literature of Ceylon* (Royal Asiatic Society prize publication) *The Commentary of the Mahavansa* (chronicle of Ceylon published by the Government of Ceylon) *The Dictionary of Pali Proper Names* (2 volumes in the Indian Historical Texts Series of the Government of India) *The Extended Mahavanna* (Pali chronicle dealing with Ceylon published by the Royal Asiatic Society of Ceylon)

Was General Editor of the Translation Series of the *Pali Buddhist Canonical Texts* under the auspices of the Buddhist Congress of Ceylon (5 volumes published)

The Government of Burma recently invited him to be General Editor of their series of English translations of Buddhist canonical texts During 1952 he lectured in several universities in the U S A under the Exchange of Persons Scheme

SARVEPALLI RADHAKRISHNAN

M A Oxford and Madras Honorary D Litt Andhra Agra Allahabad Patna and Lucknow Honorary LL D London Benares and Ceylon D L Calcutta F B A F R S L Fellow of All Souls College Oxford Hon Fellow Royal Asiatic Society Bengal Spalding Professor of Eastern Religions and Ethics Oxford University

Born on 5 September 1888 educated at Madras Christian College From 1911 to 1917 Assistant Professor of Philosophy at the Presidency College Madras then Professor of Philosophy at the Universities of Mysore (1918-21) and Calcutta (1921 31 and 1937 41) Vice Chancellor of Andhra University Waltair from 1931 36 and of Benares Hindu University from 1939 to 1948 Has held lectureships at Manchester College Oxford (1926 and 1929-30) and at Chicago University He was Hibbert Lecturer for 1929 Since 1941 he has occupied the Sir Sayaji Rao Gaekwad Chair of Indian Culture and Civilization at Benares Hindu University Lectured at Calcutta University in 1927 and 1942 and in 1946 was a visiting lecturer at the following Universities Harvard Yale

Princeton Columbia Chicago Michigan, Minnesota and Southern California

He presided at the Third Session of the Indian Philosophical Congress at Bombay in 1927 and from 1925 27 was chairman of the Congress Executive Committee In 1930 he was President of the All Asia Conference on Education held at Benares From 1931 39 he served on the League of Nations International Committee of Intellectual Co-operation From 1946-49 he was a member of the Indian Constituent Assembly was chairman of Unesco s Executive Board in 1949 and President of the Universities Commission of the Government of India in 1948 and 1949 In 1949 he was appointed Chairman of the Indian Pen Club

From 1949 to 1952 Sarvepalli Radhakrishnan served as Indian Ambassador to Moscow In 1952 he was elected Vice President of the Indian Union

His publications include *Indian Philosophy The Philosophy of Rabindranath Tagore The Reign of Religion in Contemporary Philosophy The Philosophy of the Upanishads The Hindu View of Life An Idealist View of Life East and West in Religion Eastern Religions and Western Thought Mahatma Gandhi India and China Education Politics and War Religion and Society Is this Peace? Bhaga adgita Dhammapeda*

He edited the volume *Contemporary Indian Philosophy*

ANDRÉ ROUSSEAUX

Born Paris 1896 Since 1920 has been a contributor to literary reviews and other Paris journals He has devoted himself exclusively to criticism and since the death of Henri de Régnier in 1936 has edited the literary supplement to *Figaro* The greater part of his work presents a picture of the contemporary literary scene viewed through the medium of its chief writers and includes for example *Ames et visages du XXe siècle Le Paradis perdu Litterature du XXe siècle* (3 volumes)

Rousseaux is now adding to this gallery of contemporary literary portraits a series of studies on the masters of the past of which three volumes have already appeared under the title *Le Monde classique*

In 1940 he threw in his lot with the writers who decided to resist the German occupation an attitude which he maintained for four years at first with his pen during the period of comparative freedom enjoyed for a few months by the press in the unoccupied zone then later with complete silence He put this period of retirement to good use by writing a weighty study of Péguy *Le prophète Péguy* which is now deemed to be the most important critical work published on this author During the occupation he published his

Chronique de l espérance bearing witness during the darkest hours of France s suffering of a faith that could not be shaken

Has lectured at the Sorbonne the Centre universitaire méditer ranéen and the Universities of Brussels Antwerp Liège Louvain, Namur Geneva Lausanne, Basle Zurich Freiburg Algiers Tunis Rabat Casablanca etc From January to March 1951 he visited Cairo to deliver a course of public lectures on French literature from 1900 to 1950 under the auspices of the Fuad 1 University He has also visited Alexandria Beirut and Damascus Universities and these journeys of late years in the Near East have led him to take a special interest in the problem of East West relations and to make it the subject of several lectures and articles

JACQUES RUEFF

Born 1896 Jacques Rueff received a solid mathematical training at the Ecole Polytechnique (Paris) In 1922 he published his first book *Des Sciences physiques aux sciences morales* (*Introduction a l'étude de la morale et de la politique rationnelle*) He next published his *Théorie des phénomènes monetaires* (1927) then a study that has become a classic on the hard core of unemployment (1931) In 1945 he published *L Ordre social* in which he reasserts much of his monetary theory and examines the mechanism of society in greater detail Some critics consider this work to be the foundation of a new philosophy of social evolution

In 1949 he published his *Epître aux dirigistes* and in 1951 a *Discours aux indépendants*

While still holding the chair of Political Economy at the Paris School of Political Science he has been appointed Director of the General Monetary Movements Department in the Ministry of Finance Deputy Governor of the Bank of France and Head of the Inter Allied Reparations Commission He is also Chairman of the International Council for Philosophy and Humanistic Studies and a member of the Académie des sciences morales et politiques.

HILMI ZIYA ULKEN

Born Istambul 1901 Son of Ziya Ulken Professor in the Faculty of Science Istambul After studying at Istambul University was appointed Director of Statistics at the Ministry of Education In 1933 became a university lecturer in sociology and the philosophy of history then in 1940 Professor of Sociology in the Faculty of Letters Istambul

His publications include *L éthique de l amour* (1930), *Le patri moine humanitaire* (1932), *Histoire de la pensee turque* (1933) *Les contradictions du conformisme* (1933), *Les philosophes du XXe siècle* (1936) *La sociologie générale* (1942) *La pensée de l Islam* (1946) *Les influences réciproques dans la civilisation islamique* (1947) *La morale* (1947) *La Nation et la conscience de l histoire* (1948) *Critique du materialisme historique* (1951) an introduction to his *L'expé rience totale de l homme* now in the press

At one time editor of the review *l Homme* he now fulfils this function on the *Revue de sociologie* which has published its last three issues in Turkish French and English He is one of the founders of ISA a member of the French Institute of Sociology and President of the Turkish Society of Sociology

A R WADIA

Born Bombay, 4 June 1888 graduated in philosophy at Bombay University (1909) and later obtained a Diploma in Economics and Political Science (with distinctions) at Oxford University He was called to the Bar (Middle Temple London) and read the Moral Science Tripos at Cambridge

He then held the posts of Professor of English and Philosophy and Lecturer in Psychology at Bombay University and Professor of Philosophy at Mysore University

He is a member of the Boards of Studies in Philosophy at Mysore Annamalai Agra and Baroda Universities

Was President of the Ethics Section of the Indian Philosophical Congress in 1925 of its Logic and Metaphysics Section in 1929 and of the whole Congress in 1931 Since 1937 has been Chairman of its Executive Committee

Among his publications are *The Ethics of Feminism* (Allen and Unwin) *A Textbook of Moral Instruction for Teachers* (Government of Mysore) *Zoroaster* (G Matesan and Co Madras) *Civilization as a Co-operative Adventure* (University of Madras) *Religion as a Quest for Values* (Calcutta University)

He has collaborated in the following collective volumes *Contemporary Indian Philosophy* (Allen and Unwin) *Radhakrishnan comparative studies in philosophy presented in honour of his sixtieth birthday* *The Social Philosophy of Radhakrishnan* (in the volume *Radhakrishnan* Library of Living Philosophers)

He has contributed to the following reviews In England *Mind* and *Philosophy* in the United States *The Monist* *Philosophical Review* and *International Journal of Ethics* in India *Aryan Path* *Philosophical Quarterly* etc

the lion the cat the shrew the rat the guinea pig and the chimpanzee Just as males possess the neuromuscular mechanism to mediate female sexual behavior so perhaps even to a stronger degree do the females possess the mechanism to mediate male sexual patterns

The administration of androgens to females increases the intensity of both the male and the female sexual patterns Increased intensity

TABLE 7

MASCULINE COPULATORY BEHAVIOR IN NORMAL FEMALE MAMMALS WITH AND WITHOUT ANDROGEN TREATMENT

Animal	Observations	References
Cows (in heat)	Male mounting activity	Beach[1]
Sow (estrous)	Male mounting activity	Altmann[66]
African lion (*Felis leo*) (estrous)	Male mounting activity	Cooper[67]
Cats (estrous)	Male courtship and copulatory movements	Beach[1]
Shrew (*Blarina brevicauda say*)	Mount males and execute copulatory thrusts	Pearson[68]
Rats	When in presence of estrous females normal females show male mounting and copulatory behavior	Hemmingsen[69] Ball[70] Koster[71] Beach and Rasquin[72] Beach[64]
Guinea pig (estrous or nonestrous)	Male like mounting activity	Young[73] Young Dempsey Hagquist and Boling[74]
Chimpanzee	May assume male sex role	Yerkes[75]
Rabbit	Testosterone propionate Intensified male sex behavior	Berg[78]
Dog	Testosterone propionate Intensified male sex behavior	Berg[79]
Rat	Testosterone propionate Intensified male sex behavior	Koster[71]

in masculine behavior in female rats under the influence of testosterone propionate (LXXXIX) has been reported[71,76,77] The masculine sexual behavior of adult female rabbits is intensified after testosterone propionate (LXXXIX) Similar findings have been described in the immature and adult female dog[79] the spayed female rat[80,80] and the ewe[81]

The influence of androgens in women has not been studied extensively Salmon[82] has indicated three effects of androgens in women namely increased responsiveness to sexual stimulation increased sensitivity of the external genitalia and more intense sexual gratification

accompanying intercourse Abel[83] and Greenblatt[84] have reported increased libido in women treated with androgens In some cases the hormone treatment appeared to reawaken the libido and facilitate the occurrence of orgasm Foss[85] treated women with testosterone propionate (LXXXIX) for mammary cancer and found that daily doses of 200 to 300 mg per week caused increased libido (see Chapter 18)

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CHAPTER

13

Influence on Endocrine Glands, Other than Gonads, and Various Nonendocrine Glands

The action of androgens on the secondary sex characters and the gonads has been discussed (Chapter 12) This chapter is concerned with androgen effects on the anterior pituitary and other glands of internal secretion as well as effects on nonendocrine glands and tissues such as the kidney liver heart skeletal muscle adipose tissue thymus and erythrocytes

Endocrine Glands

Anterior pituitary

Gonadectomy results in an increase in the size of the anterior pituitary an increase in the concentration of gonadotropic hormone and a change in the histological appearance of the gland As early as 1905 Fichera[1] reported an increase in pituitary weight following gonadectomy in the cock bull buffalo guinea pig and rabbit These results were confirmed in other species including the rat in which the bulk of the experimental work has been done[2] Castration in the male results in a more pronounced pituitary increase than is caused by spaying in the female[3]

Along with the increased size of the gland after gonadectomy is a change in the histology of the gland The basophilic cells increase in number and size whereas the acidophiles are decreased in number and size and regress to the chromophobic state[4] In some species as the rat certain basophilic cells tend to increase in size and vacuolate so that the nucleus and cytoplasm become crowded together at the periphery These changed basophilic cells which result from gonadectomy are known as signet cells or castration cells[5,6]

Ellison and Wolfe[7] have studied the percentage distribution of cells of the pars glandularis in the rat before and after castration Whereas pituitaries from normal rats contained 5 5 per cent basophiles and no

castration cells 55 days after gonadectomy the basophile concentration increased to 17 0 per cent and 1 4 per cent of the cells were typical castration cells In old men and old women there is a similar increase in the percentage of basophiles[8, 9]

Paralleling the increase in the size and the percentage of basophilic cells after gonadectomy there is an increase in the gonadotropic hormone content of the pituitary This increment is reported to be mostly in FSH (follicle stimulating hormone) with little change in LH (luteinizing hormone)[10] Significant increases in gonadotropic hormone content are found in the pituitaries of castrated rats guinea pigs and rabbits Parabiotic studies involving one intact immature animal, male or female and a castrated male partner have served to illustrate this relationship (Table 1) After castration the increased

TABLE 1

INFLUENCE OF CASTRATION ON GONADOTROPIC HORMONE PRODUCTION BY THE ANTERIOR PITUITARY

Experimental Animals	Parabiotic Studies Results	References
Castrated female rat Immature female rat	Precocious and enlarged ovaries.	Martins and Rocha.[11] Hertz and Meyer[12]
Castrated male rat Immature male rat	Immature rat showed hypertrophy of prostate and seminal vesicles.	Martins and Rocha.[11] McCullagh and Walsh.[14]

gonad stimulating potency of the pituitary caused enlarged ovaries and precocious estrus in normal female partners and hypertrophy of the seminal vesicles and prostate in normal immature male partners The increased production of gonadotropic hormone after gonadectomy has been established by assays of blood and urine Table 2 illustrates these findings in rodents and human beings In men castration pro

TABLE 2

INCREASED GONADOTROPIC HORMONE CONTENT OF BLOOD AND URINE AFTER CASTRATION

Subject	Finding	References
Castrated rat	FSH present in serum (negative in serum of intact animals)	Emery[14]
Castrated rabbits	FSH present in urine (negative in urine of intact rabbits)	Jeffcoate[15]
Castrated men	Increased gonadotropin in urine	Hamburger
Castrated men—2 to 20 years after castration	Increased urinary gonadotropic material (up to tenfold)	Catchpole et al[18]

CHAPTER

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Castrated men—2 to 26 years after castration	Increased urinary gonadotropic material (up to tenfold)	Catchpole et al[14]

duced increases in urinary gonadotropin as much as tenfold (Table 2).[17, 18]

These pituitary castration changes can be either reversed or prevented depending on the time at which androgens are administered. With adequate amounts of androgens administered immediately after the operation the pituitary castration effects can be completely prevented. Nelson and Gallagher[21] demonstrated this effect in rats with some thirteen steroids including testosterone (VIII) and Δ^4 androstene 3,17 dione (LXI). The experiments listed in Table 2 showing an increased gonadotropic hormone production by the pituitary of the castrated male can be reversed by the administration of androgens. Martins et al.[11, 13] prevented gonadotropin overstimulation of the gonads of parabiotic immature animals by means of a testicular mash. McCullagh and Walsh[14] used androsterone (XXV) and Hertz and Meyer[1] employed testosterone (VIII) and dehydroepiandrosterone (XXIII) with the same effect. Hellbaum and Greep[20] decreased the FSH content of the blood of castrated rats with testosterone propionate (LXXXIX).

The same relationship can be demonstrated in the human being. Thus it is well known that men with primary testicular deficiency usually excrete excessive amounts of gonadotropic hormone. The administration of the androgen testosterone propionate (LXXXIX) in therapeutically effective doses approximately 20 mg per day will decrease the urinary excretion of gonadotropic hormones to the levels found in normal man. Reduction in gonadotropin titer was found after the implantation of a 280 mg pellet of testosterone (VIII) or with 70 mg per day of methyltestosterone (XCVI) administered orally. After cessation of the androgen treatment in such patients the urinary concentration of the gonadotropic hormone returned to the pretreatment level.[18] It should be noted that doses of androgen which are lower than those above but still large enough to be clinically effective may not reduce FSH output. Thus McCullagh observed no decrease with a dose range of 75 to 150 mg testosterone propionate (LXXXIX) weekly.[119] An effect was observed however with 300 mg per week. The minimal dose of stilbestrol (CCXVI) which produced a fall was 0.5 to 2.0 mg daily. Although androgens in adequate dosages can inhibit the gonadotropic hormone production of the anterior pituitary, estrogen and perhaps an x substance from the testis may under normal conditions effect pituitary inhibitors (see Chapter 9).

There are a number of reports which indicate that androgen reduces the excessive urinary gonadotropin titer in postmenopausal or ovariec

tomized women Doses of testosterone (VIII) averaging 75 to 200 mg a week may achieve this result[1 0-122] but a lower dose range is likely to be ineffective[1 1] Estrone (XLV) injected in 1 mg doses three times a week is roughly as effective as 25 mg testosterone propionate (LXXXIX) injected according to a similar schedule[122]

It has been conclusively established that the maintenance of the gonads both testes and ovaries is dependent upon the presence of adequate concentrations of the gonadotropic hormones The administration of androgens to immature animals such as the rat is reflected in failure of gonadal development If however gonadotropins are administered along with testosterone gonadal atrophy is prevented[2] This failure of development is due to the decreased production of gonadotropic hormones by the pituitary when subjected to the inhibitory action of androgens

The pseudopregnancy reaction in the rabbit which consists of ovulation corpus luteum formation and progestational changes in the uterine mucosa is under the control of the gonadotropic hormones of the anterior pituitary This reaction can be completely inhibited by the administration of testosterone propionate (LXXXIX) undoubtedly because of a suppression of gonadotropic hormone production[23] The size of the anterior pituitary is not necessarily a guide to the gonadotropic hormone content In the male rat it has been claimed that the androgen testosterone (VIII) can cause an increase in the size of the anterior lobe at a time when the gland is producing less hormone as measured by atrophy of the testes

The evidence presented indicates that the testes and the anterior pituitary are in direct mutual relation The primary effects appear to be a stimulation of the gonads by the hormones of the anterior pituitary whereas the androgens act back on the anterior pituitary to suppress the production of the gonadotropic hormones This interrelation is basic and will be encountered frequently in the clinical discussions

Experimental exophthalmos in rabbits due presumably to a pituitary hormone is ameliorated by orchiectomy and intensified by androgen[1 4]

Adrenals

The influence of gonadectomy on the adrenal cortex has been studied in a variety of species of animals for varying lengths of time after operation Certain trends are discernible but results vary with the species the age of operation the sex and the interval between operation and study of the gland

In general the influence of gonadectomy is reflected in changes in the adrenal cortex particularly that portion of the gland known as the X zone On the basis of special histological stains a portion of the cortex appears to be different from the surrounding tissue in that the cells stain deeply with eosin and contain less cytoplasm This zone has been observed in the adrenal cortex of male mice especially during the first weeks of life and tends to disappear at sexual maturity After prepuberal castration in the male mouse the X zone persists Working with concentrates containing androgenic material Martin [4] was able to show that androgens tend to cause the premature disappearance of this zone in immature male mice The pure androgens testosterone (VIII) androstane 3α 17β diol (XXXIV) dehydroepiandrosterone (XXIII) and Δ^5 androstene 3β 17β diol (XLIX) produce similar effects in castrated male adult female and adult ovariectomized female mice [5] In these experiments it is difficult to say whether the influence is directly on the adrenal or through the anterior pituitary Gonadectomy in the female mouse has no effect on the growth or involution of the X zone but disappears rapidly during pregnancy [1, 7]

In the rat gonadectomy in the male is followed by hypertrophy of all zones of the adrenal cortex except the glomerulosa whereas ovariectomy in the female results either in no change or slight decrease in the adrenal cortex [77–79, 129] In certain experiments it was not possible to find adrenal hypertrophy after castration of the adult animal These negative results have been reported in the rat [80, 81] in the hamster [71] in the dog [72] and in the guinea pig [73, 116] The X zone of the rat is poorly developed and Howard [7] was unable to find changes in the immature rat s adrenal cortex as reported for mice

In castrated male rats the administration of a variety of androgens such as androsterone (XXV) testosterone (VIII) dehydroepiandrosterone (XXIII) and Δ^4 androstene 3 17 dione (LXI) prevents the usual castration hypertrophy of the adrenal cortex [31, 77–9, 129] The influence of androgens in ovariectomized female rats is much less intense but in the same direction as in castrated males [129]

In a study [139] made in 1948 infantile rabbits were treated with repeated injections of testosterone propionate (LXXXIV) which caused loss of lipid in the fascicular and reticular zones while the lipid content of the zona glomerulosa increased With similar hormone treatment in adult animals these results could not be observed These lipid changes were observable 2 to 4 days after cessation of hormone treatment and had completely disappeared 12 days after androgen treatment

The influence of androgens on the adrenal cortex has been studied

in human beings by quantitation of the changes in adrenocortical secretion Venning and Browne[32] were able to show that the urinary cortin was decreased as a result of testosterone propionate (LXXXIX) administration In a second study Reifenstein et al[33] demonstrated that methyltestosterone (XCVI) caused a decrease in excretion of 17 ketosteroids presumably of adrenocortical origin Methyltestosterone (XCVI) does not give rise to 17 ketosteroids The patients studied included two women with adrenal hyperplasia and Cushing's syndrome two women with adrenal hyperplasia and adrenogenital syndrome two women with normal cortical function and a man with adrenal hyperplasia and congenital absence of functioning testicular tissue The decrease in 17 ketosteroids appears to be due to pituitary inhibition with decreased production of ACTH (adrenocorticotropic hormone) which in turn causes a lowered output of adrenal steroids That ACTH does in fact cause increased 17 ketosteroid production has been demonstrated by Mason et al[34] and also by Conn[1, 3]

Large doses of methyltestosterone (XCVI) to rats produced involution of the glomerulosa thickening of the connective tissue capsule and deposits of coarse fat granules in the reticularis and fasciculata[35]

A direct influence of androgens on the adrenal cortex has been shown to exist in hypophysectomized rats Leonard[36] has shown that testosterone propionate (LXXXIX) androstane 3α 17β diol (XXXIX) and Δ^5 androstene 3β 17β diol (XLIX) are capable of decreasing the rate of atrophy of the adrenal cortex in hypophysectomized rats[36 37 116 117 130] The partial maintenance of the adrenal cortex in these experiments was due mostly to increases in cell size and not to an increase in the number of cells in the cortex In another report it was shown that although a partial maintenance was possible for about 15 days after that period the size of the adrenal cortex decreased in spite of continued treatment[37] More recently[130] the adrenal cortex was maintained by testosterone propionate (LXXXIX) in the hypophysectomized castrated rat

Large doses of adrenocortical extract or pure corticoids like cortisone produce adrenal atrophy which may be prevented by the simultaneous administration of testosterone propionate (LXXXIX)[140] This inhibitory action of the androgen acts by way of the anterior pituitary that is by preventing the corticoid from inhibiting the production and/or release of ACTH

Thyroids and parathyroids

By the use of the colchicine technique the influence of androgens on the thyroids and parathyroids has been studied[8] It was found

fed castrate mouse kidney than of the well fed castrate in spite of the fact that the action of the androgens on the accessories was identical Beland Masson and Selye[59] have studied a variety of androgens for their renotropic activity

A number of other investigators have reported stimulating effects of androgens on the mouse kidney These include Selye[49 50] Pfeiffer et al[60] Crabtree[61] and Feyel[6 63]

Kochakian[64] and Beland[59] have studied the relationship between the renotropic and androgenic effects on the seminal vesicle

Liver

In early studies of gonadectomized rats Korenchevsky and Dennison[16] showed decreases of 11 to 18 per cent in liver weight–body weight ratios as compared to those of normal rats Histological changes in the livers of castrated rats were reported and are concerned with changes in the number and size of the basophile granules[61]

After castration such androgens as androsterone (XXV) androstane $3\alpha\,17\beta$ diol (XXXIX) dehydroepiandrosterone (XXIII) and testosterone (VIII) restore the size and histology to normal[66 68] Bates Riddle and Lahr[67] were able to produce increases in weight up to 60 per cent in livers of adult pigeons after the administration of androsterone (XXV) The livers of sexually immature pullets showed decreases in total and inorganic iron when the animals were treated with testosterone propionate (LXXXIX)[147]

Heart and circulation

The influence of androgens on the heart is not without interest particularly since claims have been made for the use of testosterone (VIII) and methyltestosterone (XCVI) in the treatment of angina pectoris (Chapter 18) From the work of Korenchevsky et al[68] it appears that after castration in the rat there is a decrease in the size of the heart as well as a decrease in the potential energy of the heart muscle The administration of either androsterone (XXV) or testosterone (VIII) restores both the weight and the potential energy Testosterone propionate (LXXXIX) has been reported to raise the glycogen adenylpyrophosphate and phosphagen content of the castrated rat s heart muscle to values in the normal range[69 70]

Hamilton[74] has summarized the relationship between dermal vascularization and androgens in men Essentially it can be shown that removal of the testes causes a paling of the skin and a decreased ability of the skin to tan under the influence of ultraviolet light Androgenic

treatment produces flushing of the skin and restores the ability of the skin to tan

By means of spectrophotometric studies of the skin of men with testicular insufficiency Edwards et al[75] observed a decreased quantity of hemoglobin in most cutaneous areas and a relatively high proportion of the hemoglobin was in the reduced state Administration of testosterone propionate (LXXXIX) corrects these abnormalities within an hour of treatment Similar experiments have been reported by Reynolds et al[76] who observed rapid filling of the finger blood vessels after androgen administration to hypogonadal men

Large subcutaneous veins become less prominent and lose their taut cord like qualities after castration in men Replacement therapy reverses this state[74]

Under basal conditions the pulse rate of the castrate is slowed[74]

There is one report of hypertension being produced in rats by androgen injection[5] Subsequent experiments however have failed to reveal any significant rise or fall in blood pressure in either dogs or rats[1,8] (See also Chapter 18)

Blood

ERYTHROCYTES Hamilton[74] has studied the change in erythrocyte count resulting from castration In five men a mean decrease of 10 per cent was found 19 days postoperatively 8 per cent at 29 days and 9 per cent at 40 days Castration in rats produces a similar decrease The administration of androgens increases the red blood cell count in castrated and hypophysectomized rats[82,83] in the fowl[84,85] in castrated hamsters[86] and in eunuchoid men[87]

A small but distinct decrease in hematocrit occurs after castration along with increased erythrocyte fragility[74] Methyltestosterone (XCVI) and testosterone propionate (LXXXIX) cause an increase in the hematocrit of eunuchoid men[87] The sedimentation rate after castration in men is increased from 100 to 300 per cent[74]

HEMOGLOBIN The concentration of hemoglobin is decreased after castration and may be increased by androgen treatment This has been observed in human beings[74,87] and in rats[83]

Skeletal muscle

Skeletal muscle is known to grow at a decreased rate after castration In human beings Hamilton[74] reports that only 16 per cent of a group of 150 eunuchs (18 to 45 years of age) had skeletal musculature comparable to normal men of the same age group A similar relationship has been shown between androgens and skeletal musculature

development in a variety of species including rabbits cattle frogs[88] guinea pigs[89] and mice[90]

The temporal muscle of the castrated male guinea pig involutes and may be stimulated by a variety of androgens of which testosterone (VIII) and androstan 17β ol 3 one (XCVIII) were the most active[1]

In frogs the decreased size of the muscle after castration appears to be due to the decreased size of the individual fibers without a decrease in the number of fibers The protein content of the sarcoplasm is decreased[134]

Adipose tissue

Hamilton[74] has described the accumulation of fat in particular areas in the eunuch These sites included "the ventral abdominal wall on the area surmounting the symphysis pubis around the mammary glands on the lateral surfaces of the upper portion of the thigh and about the buttocks" He also observed the deposition of fat "over the upper aspects of the arms and the shoulders and in a few of the middle aged eunuchs over the vertebral column at about the level of the last cervical and first thoracic vertebrae At autopsy an unusual accumulation of fat was found in the mesenteries and along the posterior wall of the abdominal cavity"

Accumulation of fat in the visceral areas of the castrated rabbit[91] and the rat is well known[92, 94] In Korenchevsky's studies[92] although the castrated rat gained approximately 20 per cent less weight than the normal intact animals the animals that had been operated on had about 50 per cent more retroperitoneal fat than the control animals

Treatment of eunuchs with androgens for 6 to 8 months caused a decrease in subcutaneous fat only to increase after cessation of the hormone treatment[74]

Bone

The influence of androgens on bone growth is discussed in Chapter 15 It may be well to recall here that androgens may have an influence on the healing of fractures Principi and Bellucci[137] have shown that testosterone propionate (LXXXIX) administration to guinea pigs with fractures produces early stabilization of the callus and that within 30 days the fracture was covered with spongy osseous tissue whereas in the controls the callus contained wide zones of cartilage Testosterone propionate (LXXXIX) stimulated the cartilaginous and osseous growth of the rats penile ossicle[146] This effect was synergized by growth hormone

Van Wagenen and Hurme[1,2] treated immature rhesus monkeys with testosterone propionate (LXXXIX) and demonstrated precocious skeletal development and eruption of the canine teeth Androgen treated animals had at 2 years 10 months of age a skeletal development of about 7 years

Thymus

The thymus normally involutes at about the time of sexual maturation Castration in the rat the species that has been studied most extensively prevents this puberal involution[95-97] Administration of androsterone (XXV) dehydroepiandrosterone (XXIII) or testosterone (VIII) causes involution of thymus[98,1,9] This effect may operate through the adrenal cortex since no thymus involution could be demonstrated in the castrated adrenalectomized mouse after testosterone (VIII) administration

Miscellaneous Effects

The relation of androgens to hair growth voice changes acne and skin color in man is discussed in the clinical section Spectrophotometric examination of the skin of human castrates has shown that the content of hemoglobin and melanin is low whereas that of carotene is increased[75] These abnormalities are reversed by androgen therapy In regard to skin pigment it is of interest to note that androgen not only increases the ability of the skin of the human castrate to tan under the influence of ultraviolet light but also exerts a developing like action Thus if exposure is made to light before treatment is started no appreciable amount of pigment is deposited however subsequent administration of the hormone will lead to tanning of the previously exposed areas[101]

Testosterone (VIII) produces in the rat increased epidermal thickening and number of epithelial mitoses[1,98] Thyroxine alone has an opposite effect and a combination of the two hormones has an intermediate effect

In an in vitro study Hamilton[102] grew explants of dorsal skin obtained from 6 day old chick embryos of New Hampshire Red or Rhode Island Red fowls Addition of either testosterone (VIII) or estradiol monobenzoate (CXLIX) caused significant increases in melanophore differentiation Although sesame oil alone the solvent used for the addition of testosterone (VIII) to the culture medium was slightly active a significant increment was found over and above the oil level on the addition of testosterone (VIII) When calculated

by the 2 × 2 contingency table[104] a value of $x^2 = 7.2$ is found or a P value of less than 0.01

Ebling[144] reported the influence of sex hormones on the sebaceous glands of young female rats Estrogens caused a significant decrease in the size of glands as well as the number of cells per gland whereas androgens produced just the opposite effect an increase in size of glands and number of cells per gland

Androgens and tumors

Androgens may decrease the incidence of spontaneous tumors as well as prevent the excitatory influence of estrogens Studies have been reported on uterine cervix and lymphoid tumors Simultaneous administration of testosterone propionate (LXXXIX) and estrogens partially inhibits the ability of the estrogens to induce tumors of the uterine cervix in mice[10] Testosterone (VIII) may completely prevent the increased incidence of lymphosarcoma and leukemia in susceptible mice which follows estrogen administration Gardner et al were able to produce lymphomas in 11.9 per cent of 1799 mice in which pellets of one or more steroid or nonsteroid estrogens were implanted as compared to an incidence of 1.34 per cent in control nontreated animals When testosterone propionate (LXXXIX) was given simultaneously with the estrogen the incidence of induced tumors was reduced to approximately that of untreated controls[106,107] Testosterone (VIII) given alone did not lower the incidence below that of the controls

Nathanson and Andervont[108] using the C_3H strain of mice studied the inhibiting effect of testosterone (VIII) on mammary tumors They found a reduction of spontaneous tumors from 100 per cent to 30 per cent in groups of twenty animals Similar results with the same strain of mice have been reported by Jones[109] Heiman[110] and Loeser[111]

Lacassagne et al[112] and Gardner[106] have shown that testosterone (VIII) antagonizes the stimulating effect of estrogen on mammary cancer development in mice of the R III and C_3H strains

Testosterone (VIII) seemed to increase the incidence of spontaneous hepatomas in female C_3H mice[102] The onset of subcutaneous tumors induced by 20 methylcholanthrene in mice could be delayed for about 4 weeks and within a 12 week period decrease the percentage incidence from 42.2 to 22.3 per cent[189]

Lipschutz and co workers[113-114] have reported extensively on the antifibromatogenic action of certain steroids These compounds antagonize estrogen which is capable of inducing fibromyomatous

growths in the uterus and abdominal structures of the castrate guinea pig Antifibromatogenic action was found for testosterone (VIII) androstan 17β ol-3 one (XCVIII) progesterone (XCIV) desoxycorticosterone (CXXI) and dehydrocorticosterone (CXX) Inactive steroids include pregnane-3 20 dione (CXLVI) allopregnane-3 20 dione (CCXVII) Δ^{16} dehydroprogesterone (CLXIX) androstane 3 17 dione (LVIII) cholestenone (XXVII) androsterone (XXV) Δ^5 androstene-3β 17β diol (XLIX) androstane 3α 17β diol (XXXIX) and Δ^5 pregnen-3β-ol 20-one acetate (CCXVIII) Ethynyltestosterone (XIX) was also found to have antifibromatogenic activity one fifteenth as great as progesterone (XCIV) [114]

Androgens can promote tumor growth In man certain prostatic tumors are stimulated by androgens (Chapter 18) In experimental animals testosterone (VIII) promoted the growth of 2 acetamino fluorene mammary tumors in mice [141] and sarcomata in mice at the site of testosterone (VIII) injections have been reported.[142]

The use of androgens clinically for tumorous growths of the female sex organs is discussed in Chapter 18

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CHAPTER

14

Influence of Androgens on Metabolism and Enzymes

Protein Metabolism

General statement

The influence of androgens on protein metabolism has been studied in detail since the demonstrations by Kochakian and Murlin[1,2] and Kochakian[3] that urinary extracts containing androgenic material and also the pure compounds Δ^4-androstene-3,17-dione (LXI) and testosterone (VIII) were capable of causing nitrogen retention in the castrated dog. *Fecal nitrogen remained unchanged and no increase* in nitrogen was found in the blood, whereas the urinary nitrogen decreased. This indicated a true storage of nitrogen of about 0.05 gram of nitrogen per kilogram per day, probably in the form of protein, during the period of androgen treatment. Cessation of treatment resulted in an increase in nitrogen excretion exceeding the pretreatment levels. These experiments were followed by observations by Kenyon et al.[4] and by McCullagh and Rossmiller[5] in human beings. Administration of testosterone (VIII) or methyltestosterone (XCVI) to eunuchoid individuals produced nitrogen retention as well as progressive weight gains for as long as 40 to 70 days. These experiments were carried out during constant diet and regulated activity. When the hormone treatment was discontinued, the urinary excretion increased and for a limited period exceeded the pretreatment level. This phenomenon has been referred to as the "rebound effect."

Although the mechanism of action has not been fully elucidated, certain characteristics of the nitrogen-retaining action of androgens have been described. The quantity of nitrogen retained is too great to be explained as an action only on sex accessory tissue. Rather the effect appears to be a more general one, such as the influence on skeletal muscle (see page 209). The nitrogen-retaining action of androgens takes place in the absence of the testes, the pituitary, the pan

creas and the adrenals A variety of steroids have been found to have nitrogen retaining properties The decreased urinary nitrogen excretion is principally due to a decreased amount of urea The concentration of ammonia nitrogen is unchanged Studies on the adult *female dog indicate that there is both an increased protein synthesis* and a decreased rate of amino acid catabolism[6]

The amount of nitrogen retained under the influence of an androgen is dependent within limits upon nitrogen intake That is the greater the nitrogen intake the greater the retention and the shorter the period necessary to produce a maximum nitrogen retention In the castrate rat no change in protein retention could be demonstrated between protein contents of the diet set at 18 or 43 per cent.[7]

In young individuals there is a tendency toward a greater nitrogen *retention than in older individuals Normal individuals show a lower* nitrogen retention than individuals with hyperthyroidism panhypopituitarism dwarfism Addison's disease and eunuchoidism All the conditions have in common low urinary androgen and 17 ketosteroid titers

Dog

Tables 1 through 6 summarize the published results concerning the nitrogen retaining action of androgens and related substances *Table 1 is concerned with experiments in the dog Nitrogen retention* has been observed in normal dogs with testosterone propionate (LXXXIX) estradiol 17β (L) and estrone (XLV) The castrated dog has responded to Δ^4 androstene-3 17 dione (LXI) testosterone (VIII) and testosterone acetate (LXXIV) The depancreatized dog[8] as well as the hypophysectomized and castrated dog[9] respond to testosterone propionate (LXXXIX)

Sirek and Best[3] restudied the relationship between insulin and testosterone propionate (LXXXIX) on nitrogen metabolism of the dog These experiments were prompted by the fact that insulin has a nitrogen retaining effect when injected into the diabetic animal[24] In the totally *depancreatized dog after withdrawal of insulin for 24* hours an adequate dose of testosterone propionate (LXXXIX) produced *no effect* on nitrogen metabolism If the totally depancreatized dog was treated with insulin the androgen produced its characteristic nitrogen retention

Bartlett's studies indicated that testosterone (VIII) in dogs caused increased nitrogen storage increased the rate of protein synthesis and decreased the rate of amino acid catabolism but did not influence the size of the nitrogen pool[6]

TABLE 1

INFLUENCE OF STEROIDS ON THE URINARY NITROGEN EXCRETION IN DOGS

Compound	Status of Dog	Amount Administered (mg /day)	Nitrogen Response	References
Δ^4 Androstene-3 17-dione (LXI)	Normal male	20–60	None	2
	Castrated male	20–60	Retention	2
	Castrated male	20–60	Retention	2
	Normal male	40	None	12
Testosterone (VIII)	Castrated male	20	Retention	3
Testosterone acetate (LXXIV)	Castrated male	20–25	Retention	3
Testosterone propionate (LXXXIX)	Normal male	25	Retention	12
	Normal female	25	Retention	8
	Depancreatized female	2	Retention	8
	Adrenalectomized male	25	Precipitated adrenal cortical insufficiency	12
	Hypophysectomized castrated male	25	Retention	9
Δ^5 Androstene 3β 17β diol (XLIX)	Normal male	40	None	12
3 Methyl 1 2-cyclopentanophenanthrene (CLXXXIII)	Normal male	50	None	12
Cholesterol (XIII)	Normal male	200	None	12
7 Ketocholesterol (CLXXIX)	Normal male	500	None	12
Estradiol 17β (L)	Normal male	5	Retention	12
Estrone (XLV)	Normal male	15	Retention	12
Progesterone (XCIV)	Normal male	20	None	12

Rat

Table 2 summarizes the results on rats The administration of testosterone propionate (LXXXIX) produced nitrogen retention in normal castrate adrenalectomized and hypophysectomized animals A peculiarity of the effect in the rat is that it lasts for only a limited period (about one week) in spite of continued treatment On cessation of treatment a negative nitrogen effect is produced which is followed by a strong positive effect On a kilogram weight basis Kochakian has estimated that rats retain five times as much nitrogen as dogs or men per day A variety of androgens was studied as to their relative nitrogen retaining activity in two different strains of rats[10]

TABLE 2

INFLUENCE OF TESTOSTERONE PROPIONATE (LXXXIX) ON THE URINARY NITROGEN EXCRETION IN RATS

Status of Animal	Amount Administered (mg./day)	Nitrogen Response	References
Castrated males	1.0–7.5	Retention	9
Castrated males	Not specified	Retention	13
Normal males	Not specified	Retention	13
Adrenalectomized treated with desoxycorticosterone acetate	Not specified	Retention	13
Hypophysectomized	Not specified	Retention	13
Normal	2.5	Retention	14
Hypophysectomized	2.5	Retention	14

The nitrogen retaining activity of these compounds was strongly correlated with their androgenic potency. Studies[11] with testololactone (CLXX), a steroid with low or no androgenic activity, have indicated a significant retention of nitrogen in rats followed by a return to the pretreatment level of nitrogen excretion in spite of continued treatment.

Human being

Table 3 is a summary of experiments in human beings where free testosterone (VIII) is employed. In only one instance when the hormone was administered orally[19] were negative results reported. Significant nitrogen retention has been found in normal men, eunuchoid men, and sexually immature dwarfs.

TABLE 3

INFLUENCE OF TESTOSTERONE (VIII) IN THE URINARY NITROGEN EXCRETION IN MAN

Status of Individual	Amount Administered (mg./day)	Nitrogen Response	References
	450 mg. of pellets	Retention	15
Normal male	50	Retention	16
Normal male	90	Retention	16
Sexually immature dwarfs	20	Retention	17
Eunuchoid male	25–50	Retention	18
Cushing's syndrome 15 years—female	40 (oral)	None	19

Testosterone propionate (LXXXIX) has been widely studied for its nitrogen retaining properties (Table 4) Dosages as low as 5 mg per day have been shown to be effective When 150 to 200 mg of testosterone dissolved in human serum albumin were administered

TABLE 4

INFLUENCE OF TESTOSTERONE PROPIONATE (LXXXIX) ON THE URINARY NITROGEN EXCRETION IN MAN

Status of Individual	Amount Administered (mg /day)	Nitrogen Response	References
Eunuchoid 26–31 years—male	25	Retention	20
Eunuchoid male	5–10	Retention	21 22
Eunuchoid 21 years—male	25	Retention	15
Eunuchoid 21 years—male	25	Retention	9
Normal men 19 and 21 years	25	Retention	7
Normal man	25	Retention	12
Normal men 24 and 31 years		Retention	9
Normal men 76 years	25	Retention	23
Senile osteoporosis		Retention	24
Normal women 24 and 31 years	25	Retention	18
Addison s disease	25	Retention	19
Addison s disease 39 year —man 39 years—woman	25	Retention	25
Addison s disease 8 years—girl	25–50	Retention	26
Cushing s syndrome		Retention	24
Cushing s syndrome 15 years—girl		Retention	25
Cushing s syndrome 15 years—girl	?	Retention	10
Hypopituitary 13 years—boy		Retention	27
Sexually immature male and female dwarfs	25	Retention	23
Progeria	25	Retention	28
Thyrotoxicosis	25–100	Retention	29
Progressive muscular dystrophy	25	Retention	30
Severe chronic rheumatoid arthritis	2	Retention	31
Gastric cancer 3 men	50	Retention	32
Nephrosis	25–50	Retention	33
Senile osteoporosis	25–50	Retention	34
Postmenopausal osteoporosis	25–50	Retention	34
Cushing s syndrome osteoporosis	25–50	Retention	34

intravenously a nitrogen retaining effect was demonstrable for 8 to 10 days although no detectable hormone was present in the blood within one hour of injection and 70 to 80 per cent of the hormone could be accounted for by increased 17 ketosteroid excretion in the urine The nitrogen effect has been observed in normal men and women eunuchoid individuals patients with senile osteoporosis and

Addison's disease and patients showing Cushing's syndrome hypopituitarism *progeria, thyrotoxicosis progressive muscular dystrophy* severe chronic rheumatoid arthritis gastric cancer and nephrosis

Of interest is the ability of testosterone propionate (LXXXIX) to increase the retention of nitrogen during a period of rapid protein anabolism such as in patients recovering from chronic undernutrition The androgenic hormone may also decrease the urea excretion in male subjects on a total fast

The nitrogen retaining effect of methyltestosterone (XCVI) has been studied in some detail Table 5 lists some of the experiments

TABLE 5

INFLUENCE OF METHYLTESTOSTERONE (XCVI) ON THE URINARY NITROGEN EXCRETION IN HUMAN BEINGS

Status of Subject	Amount Administered (mg /day)	Nitrogen Response	References
Eunuchoid men	200–500	Retention	35
Eunuchoid	60	Retention	36
Normal men[4]	0	None	37
Addison's disease 8 year—girl	90	Retention	36
Addison's disease 43 years—woman	60	Retention	
	30	None	38
Simmonds' disease	100	Retention	[illegible]
Cushing's syndrome 11 years—girl	0	Retention	4
Cushing's syndrome 11 years—girl	40	Retention	39
Progeria	50	Retention	28
Hyperthyroidism	100	Retention	[illegible]
Cretin	2	Retention	40
Sexually immature dwarfs	10–30	Retention	17
Senile osteoporosis	40 100	Retention	34
Cushing's syndrome osteoporosis	40 100	Retention	34
Postmenopausal osteoporosis	40–100	Retention	34

that have been reported Positive results have been realized in normal and eunuchoid men patients with Addison's disease and Simmonds disease and patients with Cushing's disease progeria hyperthyroidism and cretinism

Table 6 lists various steroids that have been studied in the hope of finding highly active nitrogen retainers with less androgenic activity than either methyltestosterone (XCVI) or testosterone propionate

TABLE 6

INFLUENCE OF STEROIDS ON THE URINARY NITROGEN EXCRETION IN MAN

Compound	Status of Subjects	Amount Administered (mg/day)	Nitrogen Response	Reference
17 Ethyltestosterone (LXXI)	Pituitary hypofunction—children	0–40 (oral and intramuscular)	Non	17
Ethynyltestosterone (XIX)	Sexually immature dwarf boys	40 (oral)	None	40
	Addison s disease 8 years—girl	90 (oral)	Retention	26
	C hing s synd ome 50 years—wom an	1 0 (oral)	None	41
Δ^4 And te e-3 17 d o (LXI)	Sexually immat e dwarf	0	N	40
	Normal wom n 44 ye rs	15–30	N e	42
	Normal w m en 3 years	45–60	Retent n	4
Androst ro e (XXV)	P tuitary hypofun t on—children	0	None	40
	Cu hi g s synd ome 15 years—gi l	10–2	N	43
Dehydroep a d s-tero e (XXIII)	P tuitary hypofun t on	40	N e	40
	P t tary hypof nction	10–40 (acet te)	None	44
	P t tary tum	50–100 (acetate)	None	45
	C sh ng s y drome 15 years—gi l	2	None	33
Δ^5 And t ne-3β 1 β-l l (XLIX)	Senile osteoporosis — nan	60	Sl gl t re-tent on	4
	Cushing s synd me 58 years—wom n	30	N e	46
		45	Sl ght re-tent n	
	Sex ally mmature dwarf	10	Slight re-tent on	
		45–100 (d cetate)	Slight re-te t n	17
17 Methyl Δ and o-t e-3β 17β-d l (CXXXIII)	Addison d se se 8 y rs—girl	50	Retent n	6
	Se u lly immature d rf boys	10–50 (ral ntra muscular)	R tentio (nable)	17
And ostane-3α 1 β-d ol (XXXIX)	N rmal m n	10	Retent on	47
	Cu hing s syndrom	10 7	Rete t on	24
	Add son disease	40–80 (o al)	I creased e cret on	38
	Se u lly mm ture boy	30–100 (d etate)	Retention	1
17 Methyl dro t e-3α 17β-d l (CXL)	Eunu h d	60 (oral)	Rete t on	48
	Addison disease—women	40 (ral)	Retent n	33
	Addis n disease—w m n	40–80 (o l)	None	38
	Boys	30–50 (ral)	Retent on	17
Δ^5 P gnen 3β-ol 20-o e (XI)	N m l men	100	Retent n	49

(LXXXIX) These compounds are 17 ethyltestosterone (LXXI) Δ^4 androstene 3 17 dione (LXI) androsterone (XXV) dehydroepiandrosterone (XXIII) Δ^5 androstene 3β 17β diol (XLIX) 17 methyl Δ androstene 3β 17β diol (CXXXIII) androstane 3α 17β diol (XXXIX) 17 methylandrostane 3α 17β diol (CXL) and Δ^5 pregnen 3β ol 20 one (XI) From the data presented it appears that the nitrogen retaining activity of a given steroid was correlated with its andro

genicity 19 Nortestosterone (CLXXI) has recently been shown to have a high activity in a levator ani muscle test and relatively low androgenic activity[50] This compound is a promising one for studies of nitrogen retaining activity Other promising compounds include testololactone (CLXX)[11] and 1 androstan 6β ol 17 one (XL)[147]

From the summaries it appears that testosterone propionate (LXXXIX) and methyltestosterone (XCVI) produced the greatest nitrogen retention whereas androstane-3α 17β diol (XXXIX) ethynyl testosterone (XIX) Δ androstene-3β 17β diol (XLIX) and 17 methyl Δ^5 androstene 3β 17β diol (CXXXIII) produced nitrogen retention of a lower order The other compounds studied appeared to be very weak or entirely inactive

The body growth of castrated mice may be stimulated by testosterone (VIII) or by growth hormone When both hormones are administered simultaneously the effects are summated[51]

Carbohydrate Metabolism

A few isolated studies on carbohydrate metabolism have been reported An early study indicated that testosterone propionate (LXXXIX) in male rabbits caused hyperglycemia and a decrease in liver glycogen[106] Gaunt et al[134] were unable to influence liver or muscle glycogen in rats by treatment with testosterone propionate (LXXXIX) On the other hand Cahone[137] claimed a decreased concentration of muscle glycogen in guinea pigs treated with testosterone (VIII) Testosterone propionate (LXXXIX) caused no change in the muscle glycogen of castrated rats but a decrease in adrenalectomized animals

Lewis and McCullagh[1] reported that methyltestosterone (XCVI) produced a decrease in sugar tolerance and a decreased liver glycogen in the intact rabbit Hypophysectomy or thyroidectomy nullified the effect Testosterone (VIII) produced no change in tolerance but liver glycogen was reported to be increased In hypogonadal patients these workers reported decreased sugar tolerance and glycogen stores

Shorr et al[98] have reported a decreased urinary excretion of citric acid in a man with pituitary hypogonadism treated with testosterone (VIII)

Under the influence of androgens fructose and citric acid tend to accumulate in the male accessory sex glands[130 x] This response has been suggested as a sensitive indicator for androgenic activity[109 10]

Castration causes a decreased concentration of phosphocreatine

ATP and glycogen of the heart muscle which may be restored to normal by testosterone propionate (LXXXIX)[139]

Creatine and Creatinine

Our knowledge of the metabolism of creatine and creatinine has recently been enriched by isotope experiments Glycine reacts with arginine to form an intermediary compound glycocyamine The glycocyamine is methylated to form creatine Creatine in turn may be converted to creatinine and excreted in the urine Creatinine on the other hand cannot be converted back to creatine Creatine in combination with phosphoric acid forms creatine phosphate which plays an important role in carbohydrate metabolism of muscle

Androgens such as testosterone (VIII) tend to cause urinary retention of creatine whereas methylated androgens such as methyl testosterone (XCVI) produce creatinuria This phenomenon in various animals is discussed in the following sections

Rodent

In the rabbit castration causes immediately after operation an increased excretion of both creatinine and creatine Androgens can decrease the creatinuria and probably the creatininuria although the latter point has been challenged Schrire and Zwarenstein[5] claim it can be abolished but Buhler[63] has been unable to demonstrate this effect The creatinuria which follows castration in the rabbit spontaneously disappears in about one month[108] which may be due to the adrenal androgens

It has been reported that androgens can prevent creatinuria in the castrated rat caused by feeding creatine[4] Coffman and Koch[55] likewise found that the creatinuria induced in rats by feeding creatine can be diminished by testosterone propionate (LXXXIX) in both normal or castrated animals This androgen also causes increased retention of exogenous creatine by skeletal muscle[109]

Monkey

Jailer[56] found that 5 mg per day of testosterone propionate (LXXXIX) could decrease or completely abolish the creatinuria of immature or castrated mature male monkeys and androgen also restored the ability of the animal to retain administered creatine Jailer[57] was also able to decrease or abolish the intense creatinuria caused by the administration of thyroxine to monkeys

Human being

With doses of testosterone propionate (LXXXIX) in the range of 20 mg per day in normal children there appears to be a decrease in creatinuria but little change in creatinine excretion.[110] Testosterone (VIII) inhibits both spontaneous creatinuria or creatinuria produced by feeding creatine. Hoagland et al.[110] have made the interesting observation that no decrease in creatinuria could be induced by testosterone (VIII) in boys suffering from progressive muscular dystrophy in contrast to the findings in normal children. Actually the urinary creatine level remained normal during treatment and rose temporarily to levels above normal upon cessation of treatment. Creatinine excretion remained essentially unchanged during treatment in both the normal and the dystrophy patients.

Wilkins, Fleischmann and Howard[54] reported that methyltestosterone (XCVI) caused an increased creatinuria when used as an androgen for the treatment of dwarfed children. The effect was observed after a latent period of 4 to 16 days and was maintained for months. Creatinuria can be produced also by other methylated steroids such as 17-methyl-Δ^5-androstene-3β,17β-diol (CXXXIII) and 17-methylandrostane-3α,17β-diol (CXL). Among the ineffective steroids are androsterone (XXV), dehydroepiandrosterone (XXIII), Δ^4-androstene-3,17-dione (LXI), testosterone propionate (LXXXIX), Δ^5-androstene-3β,17β-diol (XLIX), androstane-3α,17β-diol (XXXIX) and 17-ethyltestosterone (LXXI). No correlation was found between the ability of a compound to produce creatinuria, nitrogen retention and action of a steroid on male accessories. Increased blood levels of creatine and guanidoacetic acid were found in men and women as well as increased urinary concentrations after methyltestosterone (XCVI) treatment. Testosterone (VIII) was inactive.

This effect has in addition to dwarfed children been observed in normal children, children suffering from progressive muscular dystrophy,[110] normal men,[111] eunuchoids[112] and patients with thyrotoxicosis.[1]

Attempts by Wilkins and Fleischmann[4] to inhibit the creatinuria caused by methyltestosterone (XCVI) with an equal amount of testosterone propionate (LXXXIX) failed.

Methyltestosterone (XCVI) causes an increased excretion of glycocyamine along with creatinuria.[19] This is in keeping with the idea that this androgen actually increases the synthesis of creatine.

Samuels et al.[9] believe that the primary site of the action of methyltestosterone (XCVI) is on the kidney. In severe liver disease methyl

testosterone (XCVI) was able to produce increased quantities of creatine This was not possible in nephrosis

Electrolytes

Thorn and Harrop[58] have reported that testosterone (VIII) and the propionate (LXXXIX) were effective in causing sodium retention in the normal dog The activity was of a low order A single dose of 125 mg of the propionate or repeated doses of 25 mg were required Doses of 40 mg of Δ^5 androstene 3β 17β diol (XLIX) or Δ^4 androstene 3 17 dione (LXI) were without effect in the normal dog

The observations of Kenyon[61] and Kenyon et al[20] indicated that when eunuchoids were treated for a long period of time with testosterone propionate (LXXXIX) an edema was observed The urine during this period showed a decreased concentration of sodium chloride potassium and phosphorus[18] The red blood cell count the cell volume and the plasma protein concentration remained normal The serum levels of sodium chloride and potassium remained constant Effects of a similar nature have been demonstrated with methyltestosterone (XCVI) androstane 3α 17β diol (XXXIX) and 17 methylandrostane 3α 17β diol (CXL) in normal individuals and in patients with Simmonds disease and Addisons disease

Atherosclerosis

The fact that eunuchs are highly resistant to coronary atherosclerosis[140] and men under 40 years of age have this disease ten to twenty four times more frequently than women[141] led naturally to inquiries as to the role of the sex hormones No definitive statements can be made with respect to the disease in man but research in chicks by Katz and his group[14] has demonstrated beyond question that experimental atherosclerosis in this species can be reversed by estrogen treatment Androgens administered to chicks on atherosclerosis producing diets did not intensify the disease nor did the androgens inhibit the beneficial effects of estrogen treatment[143] Fox[144] has reported that wild ground fowl show atherosclerosis and that incidence is 9 1 in favor of males a pattern that is similar to that found for human beings

Lewis et al[145] have observed two abnormal low density lipoprotein components in the serum of immature castrated rabbits treated with testosterone and they suggest that this "may offer a partial explanation for the greater susceptibility of males than females to atherosclerosis"

Basal Metabolism and Respiratory Quotient

Studies on dogs indicated that androgens caused a small increase in the basal metabolic rate and a tendency toward a lowered R.Q in "fat" castrated dogs but not "thin" castrated dogs[114] Neither testosterone (VIII)[115] nor methyltestosterone (XCVI)[116] produced a change in the basal metabolism of castrated rats Small increases were noted in thyroidectomized castrated rats[116] Testosterone (VIII) tended to cause increments in the basal metabolic rate in human subjects after latent periods of 6 to 60 days[117 118] McCullagh and Rossmiller[62] and Jones McCullagh et al[45] have reported striking increases in the basal metabolic rate (up to 54 per cent) after the oral administration of methyltestosterone (XCVI) to one eunuch and nine eunuchoid men Simultaneously there was a lowering in the R Q Similar findings with methyltestosterone (XCVI) have been found in pituitary dwarfs[1] and in patients with Simmonds disease[1 2] Kinsell Hertz and Reifenstein[3] could not increase the basal metabolic rate of hyperthyroid patients treated with methyltestosterone (XCVI)

Oxidative Metabolism and Enzyme Concentrations

Gordan and Elliott[63] reported that any of a group of steroids including testosterone (VIII) could inhibit aerobic respiration of rat cerebral cortex homogenates Desoxycorticosterone (CXXI) produced the most intense inhibition The inhibitory action of the various steroids paralleled their anesthetic activity as described by Selye[64] Subsequent studies by this group of workers (Eisenberg et al[6]) showed that the oxygen uptake of rat brains was increased by castration and that castration plus androgen treatment prevented the increment in brain oxygen uptake Testosterone (VIII) added in vitro could inhibit the Qo_2 of brain cells from normal castrated or castrated testosterone treated animals

Although castration had a profound influence on brain oxygen uptake no such effect could be demonstrated for the liver diaphragm or levator ani muscle (Eisenberg et al[66]) However castration did render the diaphragm muscle and liver tissue insensitive to the oxygen uptake inhibiting action of testosterone (VIII) This insensitivity could be reversed by the in vivo treatment of the castrate rat with testosterone (VIII)

The influence of steroids on the oxygen uptake of tissues was studied by Hayano et al[67] Liver kidney and brain tissues were studied as tissue slice preparations and as homogenates Desoxycorticosterone (CXXI) dehydroepiandrosterone (XXIII) methyltestosterone

testosterone (XCVI) was able to produce increased quantities of creatine This was not possible in nephrosis

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Table 7 summarizes the data on observed changes in succinic dehydrogenase and succinoxidase content of tissues as influenced by androgens with and without estrogens

Arginase

Arginase has the specific function of hydrolyzing arginine to ornithine and urea The relationship between arginase concentration of liver and kidney tissue and steroid hormones is summarized in Table 8

Administration of androgens produces a profound increase in arginase concentration of the kidney but no significant influence on liver or intestinal concentration Castration in the mouse produced a slight increment in kidney arginase concentration mainly due to the slight decrease in kidney weight Most steroids which increase the size of the castrated mouse kidney also increase the arginase concentration of this tissue A particularly interesting phenomenon is demonstrated in Fig 1 illustrated by Kochakian's original data[72] As the dose of

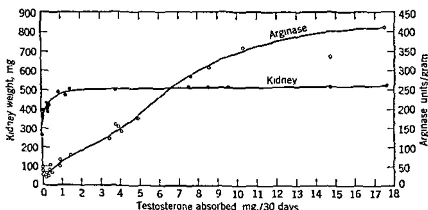


Fig 1 Influence of testosterone on the weight and arginase content of the kidney (Kochakian [2])

testosterone (VIII) was increased the castrated mouse kidney increased approximately 100 per cent whereas the arginase concentration of the tissue increased some 600 per cent Furthermore a maximum increment in tissue weight was attained at a dose of 2 mg of testosterone (VIII) for a 30 day period while the arginase concentration kept increasing up to a dose level of 18 mg for the same period After the administration of low concentrations of certain androgens to the castrated mouse actual decreases in kidney enzyme concentration have been noted at a time when the kidney is increasing rapidly

(XCVI) and testosterone (VIII) consistently inhibited oxygen consumption at concentrations of the order of 2×10^{-3} M or less No correlation of the magnitude of these inhibitors with the androgenic protein anabolic or renotropic activity was apparent Modification of the steroid structure on the other hand appeared to determine in a small way the extent of the suppression Those steroid containing keto groups were in general more inhibitory than those that had only hydroxyl functions Hormonally inactive steroids were inactive with respect to oxygen consumption

Kochakian[68] has demonstrated that testosterone (VIII) (0 28 mM) which is capable of inhibiting the respiration of many tissues does not have this effect on the Brown Pearce epithelioma

Dirscherl and Hauptmann[69] have reported that small amounts of androgens and estrogens stimulate anaerobic glycolysis and respiration of liver slices

Succinic dehydrogenase and succinoxidase

In the presence of a hydrogen acceptor the enzyme succinic dehydrogenase oxidizes succinic acid to form fumaric acid The succinoxidase system consists of succinic dehydrogenase plus cytochrome oxidase The concentration of this enzyme system in some tissues has been shown to be a function of steroid hormones or more specifically androgen concentration In both seminal vesicles and prostate there is a decrease in enzyme concentration after castration which may be restored to normal by effective doses of testosterone (VIII) or testosterone plus estradiol (L) (Davis et al[70]) On the other hand Leonard[71] has shown that the levels of this enzyme in the perineal musculature remain unchanged after castration of the rat and after the administration of androgens

TABLE 7

INFLUENCE OF STEROID HORMONES ON SUCCINIC DEHYDROGENASE (SD) IN THE RAT[23]

Condition	Gland	Change in SD	References
Castration	Prostate and seminal vesicles	Decrease	70
Castration + testosterone (VIII)	Prostate and seminal vesicles	Increase	70
Castration + testosterone (VIII) + estradiol 17β dipropionate (CIXXX)	Prostate and seminal vesicles	Increase	70
Castration	Perineal musculature	No change	71
Castration + androgen	Perineal musculature	No change	71

in size As the dose is further increased the arginase concentration quickly increases

From Kochakian's data dealing with the influence of androgens on mouse kidney arginase concentration three categories of responses depending upon the androgen administered can be discerned (Table 9)

TABLE 9

QUALITATIVE DIFFERENCES IN WEIGHT AND ARGINASE RESPONSES OF MOUSE KIDNEY TO DIFFERENT ANDROGENS[23]

	Low Dose Effect		High Dose Effect	
Typical Substance	Kidney Weight	Change in Arginase Concentration	Kidney Weight	Change in Arginase Concentration
Testosterone (VIII)	Fast maximum increase	Initial decrease	Leveling off	Increase beyond tissue weight increase
Methyltestosterone (XCVI)	Fast maximum increase	Fast initial increase (no decrease)	Leveling off	Increase beyond tissue weight increase
Androstane-3β 17β-diol (CXXIV)	Fast low maximum increase	Decrease	Leveling off at low level	Prolonged decrease

Experiments by Kochakian[68] showed that phlorizin treated rats on a 70 per cent protein diet showed an increase in arginase proportionate to kidney weight When androgen was administered to these animals a further increment in kidney arginase was observed Furthermore rats made diabetic with alloxan and having sclerotic kidneys responded to testosterone propionate (LXXXIV) with the typical kidney weight and arginase increment Cortisone (CXVI) produced an immediate increment in kidney arginase whereas the liver arginase increased after an initial delay

Fraenkel Conrat et al[73] studied the influence of adrenalectomy and hypophysectomy on rat liver arginase concentrations Adrenalectomized hypophysectomized or normal rats treated with corticosterone (CXIX) or 11 dehydrocorticosterone (CXX) showed increased liver arginase concentration whereas similar animals treated with desoxy corticosterone (CXXI) did not show these changes

Kochakian[72] has shown that mice in a state of undernutrition still show changes in arginase content of tissues similar to well fed animals Under these nutritive conditions castration produced an increase in kidney enzyme concentration which was further increased by the ad

TABLE 8

Influence of Steroid Hormones on Arginase Content of Tissues[33]

Species	Condition of Animal and Treatment	Tissues Studied	Change in Arginase Content	References
Mouse	Castration	Kidney	Increase	76
	Castration + testosterone propionate (LXXXIX)	Kidney	Increase	76
Rat	Adrenalectomy and hypophysectomy	Liver	Decrease	73
	Normal hypophysectomy or adrenalectomy + cortisone (CXVI) *corticosterone (CXIX) or 11-dehy*drocorticosterone (CXX)	Liver	Increase	73
	Normal hypophysectomy or adrenalectomy + desoxycorticosterone (CXXI)	Liver	No change	73
Mouse	Castrated + cortisone (CXVI) or 11-dehydrocorticosterone (CXX)	Liver	Increase	91, 92
		Kidney	Increase	91, 92
Rat	Castration + testosterone propionate (LXXXIX)	Liver	No change	91, 92
		Kidney	Increase	91, 92
	Hypophysectomy	Liver	Decrease	91, 92
		Kidney	Decrease	91, 92
	Hypophysectomy (male) + testosterone propionate (LXXXIX)	Liver	No change	91, 92
		Kidney	Increase	91, 92
	Adrenalectomy	Liver	Decrease	77
		Kidney	Decrease	
	Adrenalectomy + saline	Liver	No change	77
		Kidney	No change	
	Adrenalectomy + desoxycorticosterone (CXXI)	Kidney	Slight increase	77
	Adrenalectomy + adrenal cortical extract	Liver	No change	77
		Kidney	Slight increase	
	Adrenalectomy + testosterone propionate (LXXXIX) + adrenal cortical extract	Liver	No change	77
		Kidney	Increase	[illegible]
	Castrated male + testosterone propionate (LXXXIX)	Liver	Increase	
		Intestine	Increase	93
		Kidney	Increase	
	Castrated male + testosterone propionate (LXXXIX)	Liver	Decrease	
	Normal male + testosterone propionate (LXXXIX)	Liver	Increase	
Hamster	Castrated male + testosterone propionate (LXXXIX)	Kidney	Decrease	8
		Liver	None	78
Guinea pig	Castrated male + methyltestosterone (XCVI)	Kidney	Small increase	79
		Liver	None	

lism as well as bone formation Influences of the steroid hormones on acid and alkaline phosphatases have been reported

Tables 10 and 11 summarize representative samples of the experimental findings Kochakian [a] has made an extensive study of the influence of steroid hormones on the phosphatase content of the mouse

TABLE 10

INFLUENCE OF ANDROGENS ON ALKALINE PHOSPHATASE CONCENTRATIONS[a]

Species	Condition Sex and Treatment	Tissues Studied	Change	References
	Gland Removal			
Rat	Castrated male	Kidney	Increase	91
		Liver	Slight increase	
Rat	Castrated male	Seminal vesicle	Decrease	85
		Prostate	Increase decrease (8 days)	
Mouse	Ovariectomized female	Uterus	Decrease	96
		Vagina	Decrease	
Rat	Hypophysectomized male	Liver	Increase	31
		Kidney	Decrease	
Mouse	Castrated male	Kidney		76
		Liver		
		Intestine		
	Androgen Treatment			
Mouse	Castrated male Testosterone (VIII) and other androgens	Kidney	Decrease	72
Rat	Hypophysectomized male Testosterone	Kidney	Increase	31
		Liver	No change	
Rat	Male Testosterone (VIII)	Femur	Increase	97

kidney Castration in the mouse does not affect the total amount of *kidney alkaline phosphatase* but increases the concentration This is due to the fact that the mouse kidney suffers involution after castration On the other hand the acid phosphatases show a decrease which is proportional to the tissue mass Thus in the case of the acid phosphatases no change in concentration is observed

Testosterone (VIII) treatment of the castrated mouse results in an increase in kidney size and a striking decrease in the concentration of alkaline phosphatases Actually the total alkaline phosphate is decreased The total acid phosphatase content of the kidney is increased but only a shade greater than the increase in kidney size This results in only a slight increment in acid phosphatase content of the testosterone stimulated kidney Treatment of the normal mouse with andro-

ministration of androgens such as testosterone (VIII) and methyltestosterone (XCVI)

Such androgens as testosterone (VIII) and methyltestosterone (XCVI) produced the most dramatic increases in enzyme concentrations But others produced less significant increases or as in the case of epiandrosterone (XXI) a slight decrease Estradiol 17β (L) produced a moderate increase as did cortisone Both progestational substances studied progesterone (XCIV) and ethynyltestosterone (XIX) produced slight decreases

Growth hormone does not influence the concentration of kidney arginase in castrated mice and can inhibit the usual stimulating effect of testosterone propionate (LXXXIX)[133]

Amino acid oxidase

Clark et al[74] showed that castration in the mouse resulted in a decreased D amino acid oxidase content of kidney tissue but not of liver or intestine Adequate treatment of the castrated mouse with testosterone propionate (LXXXIX) restored the kidney oxidase content to normal or above normal levels

Cytochrome oxidase

Treatment of castrated rats by testosterone propionate (LXXXIX) results in an increased content of cytochrome oxidase in the seminal vesicles and prostate (Davis et al[70])

Cholinesterase

Cholinesterase hydrolyzes acetylcholine into choline and acetic acid Everett and Sawyer[75] studied the influence of gonadectomy and sex hormone replacement therapy on the cholinesterase content of blood in the rat Wattenwyl et al[146] found that the serum cholinesterase of sexually mature male guinea pigs decreases after castration but may be brought back to normal by subcutaneous implantation of testosterone (VIII) This is in conflict with the results of Everett and Sawyer who found an increase in serum cholinesterase after castration and treatment of the castrated rat with androgen produced a decrease in enzyme concentration Further work is needed to show if this discrepancy is due to species difference

Phosphatases

This group of enzymes catalyzes a variety of reactions which are concerned with carbohydrate nucleotide and phospholipid metabo

phosphatase concentration of the kidney has been found to be qualitatively similar

The relationship of steroids and the concentration of phosphatases in male accessory tissues has been studied in some detail especially with respect to the prostate Kutscher and Wolberg[80] reported a high content of acid phosphatase in human adult prostatic tissue Gutman and Gutman[81] confirmed the earlier finding and showed that the preputial gland had a similarly high content of enzyme in contrast to the relatively low concentration of enzyme in the testis Cowpers gland liver and kidney

Huggins et al[83] showed that the acid phosphatase content of dog prostatic secretion was conditioned by androgens The secretion of castrated dogs was significantly lower in acid phosphatase content than that of normal dogs and the decrease could be reversed by adequate treatment with testosterone propionate (LXXXIX) Gutman and Gutman[8] obtained similar results in the monkey

Of particular interest is the change in serum acid phosphatase in individuals suffering from osseous metastases of a malignant prostate In such individuals castration or treatment with estrogens produced a drop in acid phosphatase (Huggins et al[83]) As might be expected androgen treatment under the same conditions produced immediate rises in serum acid phosphatases (Huggins and Hodges[84])

Stafford et al[85] showed that concentrations of both acid and alkaline phosphatases of seminal vesicles are decreased by castration as early as the fourth day postoperatively The concentrations of both phosphatases of the seminal vesicles are restored to normal by testosterone propionate (LXXXIX) In the prostate a somewhat different situation is found Although at 8 days postcastration the concentrations of both phosphatases are decreased at 4 days postoperatively a distinct increment in both acid and alkaline phosphatase was found At 4 days the administration of testosterone propionate (LXXXIX) produced a decrease in acid and alkaline phosphatase as compared with the castrated uninjected control The action of testosterone (VIII) was reversed 8 days postoperatively when the prostates of the operated animals were low in phosphates At this time the administration of the androgen produced a distinct increase in acid and alkaline phosphatase concentrations

Vesiculose

Vesiculase is an enzyme which is present in that portion of the rat anterior prostate frequently called the coagulating gland which causes the coagulation of a protein like substance secreted by the seminal vesicles[10 0 103 4] Normally mammalian semen is ejacu

TABLE 11

STEROID INFLUENCES ON ACID PHOSPHATASE CONCENTRATIONS[33]

Species	Condition of Animal and Treatment	Tissues Studied	Change	References
Mouse	Normal and castrated Testosterone (VIII) and other androgens	Kidney	Increase	76
	Castrated male	Kidney Liver Intestine	No change	76
Rat	Castrated male	Kidney	No change	91
	Hypophysectomized male	Liver	Slight decrease	91
		Kidney	Decrease	
	Castrated male	Seminal vesicles	Decrease	85
		Prostate	Increase (4 days) decrease (8 days)	85
	Hypophysectomized male (testosterone)	Liver Kidney	No change No change	91
	Castrated male	Seminal vesicles	Increase	85
	Testosterone propionate (LXXXIX)	Prostate	Decrease (4 days)	
Guinea pig	Castration	Liver Kidney	No change	79
Dog	Castration	Prostatic secretion	Decrease	94
	Castration + testosterone propionate	Prostatic secretion	Increase	94
Human being	Men—osseous metastases in prostatic cancer + castration or estrogen	Serum	Decrease	83
	Men—osseous metastases in prostatic cancer + androgens	Serum	Increase	84

gens shows a picture of kidney phosphatase similar to that of the castrated animal

The phosphatases of liver and intestines are not influenced by androgens

In addition to the study on the kidney of the mouse there are data on the rat[7, 1] the hamster (Kochakian et al[78]) and the guinea pig (Humm et al[79]) In all these rodents the influence of androgens on

phosphatase concentration of the kidney has been found to be qualitatively similar

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Vesiculase

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lated in liquid form In the rodent rat and guinea pig a striking semen coagulation occurs soon after ejaculation This phenomenon can be reproduced by the mixing of seminal vesicle fluid with vesiculase in vitro After castration in the rodent the protein substrate is not produced in sufficient quantity to permit normal coagulation[105] but may be reversed by androgen treatment

β Glucuronidase

Testosterone propionate (LXXXIX) increases the kidney β glucuronidase of male female and castrated mice The enzyme content

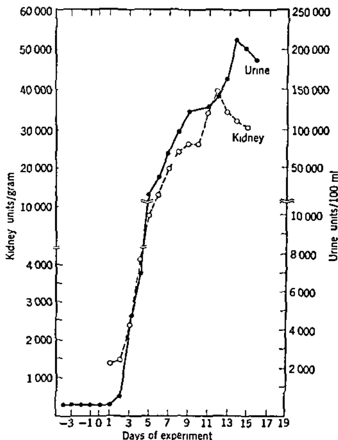


Fig 2 Influence of testosterone on the β glucuronidase content of kidney tissue and urine (Riotton and Fishman[126])

of the seminal vesicles of castrated mice increased and administration of the hormone neutralized this effect[1] Testosterone (VIII) increased the urinary β glucuronidase as well as the content in the kidney

tubules[1,6] (Fig 2) Androgens also increase the β glucuronidase content of the spayed rat uterus[3,9]

Androgens and Specific Enzyme Systems

D Amino acid oxidase

The D amino acid oxidase system is inhibited by desoxycorticosterone (CXXI) and other steroids including androgens (Hayano et al) The steroid inhibition was not specific for substrate D-alanine alone since similar results were obtained with *dl* isoleucine and *dl* methionine The action of the steroid on the enzyme is reversible It is possible to regenerate an active preparation by means of acetone precipitation of the enzyme This treatment removes the steroid and regenerates a completely active enzyme

Desoxycorticosterone (CXXI) was the most potent free steroid with respect to inhibition The influence of a variety of steroids is described in Table 12 In the adrenocortical series no correlation could be found between inhibitory activity and polarity Thus hydrocortisone (CXV) the most polar in this series yielded an inhibition ratio of 0 25 (see Table 12) Hormonally inactive steroids such as cholesterol (XIII) 20 21 epoxy Δ^4 pregnen 3 one (CLXII) pregnane-3α 20α diol (XCV) and Δ^4 pregnene 17α 20α diol-3-one (CCV) had no inhibitory activity Even the sodium cholesterol sulfate (CIX) was inactive This is in contrast to the finding that such steroids as estrone (XLV) estradiol 17β (L) and dehydroepiandrosterone (XXIII) although completely inactive or possessing modest activity as the free compound show high activity as the sodium sulfate ester

Substances like testosterone (VIII) produce only a slight inhibition (19 per cent) when the system is complete at zero time as compared with 53 per cent inhibition if a preincubation period of 30 minutes at 38 C is permitted

α Glycerophosphate dehydrogenase

Hochster and Quastel[8] have studied the influence of a variety of steroids on the anaerobic and aerobic oxidation of α glycerophosphate The enzyme preparations were derived from both yeast and rat liver Androgens and other steroids have an in vitro inhibitory action of the α glycerophosphate dehydrogenase system 3 Ketosteroids possess the highest inhibitory activity whereas 17 and 20 ketosteroids possess activity but at a reduced level Brain homogenates are capable of neutralizing the steroid inhibition of the yeast dehydrogenase system

TABLE 12

COMPARATIVE ACTIVITY OF VARIOUS STEROIDS ON D-AMINO ACID OXIDASE[138]

$$\text{Ratio} = \frac{\text{Inhibition produced by steroid}}{\text{Inhibition produced by 1 mg. Desoxycorticosterone (DC)}}$$

Steroid	Concentration	Mean Inhibition % (Range)	Mean Inhibition of Desoxycorticosterone (1 mg.) Run Simultaneously % (Range)	Ratio = Steroid/DC
		C_{21} Steroids		
Progesterone (XCIV)	1.0	37 (31–44)	82 (68–97)	0.45
Ethynyltestosterone (XIX)	1.0	5 (3–6)	86 (80–9[illegible])	0.06
Desoxycorticosterone acetate (CLXXXI)	1.0	18 (11–25)	90 (77–100)	0.20
Desoxycorticosterone glucoside (CLXXXII)	1.0	34 (22–46)	90 (83–97)	0.38
Corticosterone (CXIX)	1.0	14 (3–16.3)	69 (64–84)	0.20
Dehydrocorticosterone (CXX)	1.0	16	84	0.19
17α-Hydroxy-11-desoxycorticosterone (CXVII)	1.0	0 (9–8)	65 (57–73)	0.0
Hydrocortisone (CXV)	1.0	14 (13–14)	57	0.25
Cortisone (CXVI)	1.0	35	87	0.40
Allopregnane-3β,17α,21-triol-20-one (CVII)	1.0	6	84	0.07
		Androgens		
Sodium androsterone sulfate (LXXVIII)	1.0	55 (52–57)	85 (78–92)	0.65
	2.0	81	92	0.88
Sodium dehydroepiandrosterone sulfate (LXXX)	1.0	55 (51–58)	85 (78–92)	0.65
	2.0	86	92	0.94
Testosterone (VIII)	1.0	10 (−2–18)	77 (49–100)	0.13
Androsterone (XXV)	1.0	10 ([illegible]–20)	86 (80–9[illegible])	0.1[illegible]
Dehydroepiandrosterone (XXIII)	1.0	12 ([illegible]–18)	75 (64–80)	0.16
Δ^4-Androstene-3,17-dione (LXI)	1.0	9 (6–11)	71 (43–92)	0.13
Androstane-3α,17β-diol (XXXIX)	1.0	0 (−5–4)	80 (80–[illegible])	0.00

TABLE 12 (*Continued*)

COMPARATIVE ACTIVITY OF VARIOUS STEROIDS ON D-AMINO ACID OXIDASE [a]

$$\text{Ratio} = \frac{\text{Inhibition produced by steroid}}{\text{Inhibition produced by 1 mg Desoxycorticosterone (DC)}}$$

Steroid	Concentration	Mean Inhibition % (Range)	Mean Inhibition of Desoxycorticosterone (1 mg.) Run Simultaneously % (Range)	Ratio = Steroid / DC
Δ^5 Androstene-3β 17β diol (XLIX)	1.0	7 (5–10)	92 (92–97)	0.08
Methyltestosterone (XCVI)	1.0	−8 (−16–2)	90 (77–100)	−0.08
17α Hydroxyprogesterone (LIX)	1.0	3 (2–3)	92 (92–92)	0.03
		Estrogens		
Sodium estrone sulfate (CLVII)	0.1	18	80	0.22
	0.2	28	80	0.35
	0.5	58	80	0.72
	1.0	96 (96–96)	80 (80–80)	1.20
	2.0	98	80	1.23
Sodium estradiol sulfate (CLVIII)	1.0	86 (76–95)	86 (80–92)	1.00
	2.0	97	80	1.21
Sodium equilen sulfate (CLIX)	1.0	86	64	1.34
	2.0	100	64	1.56
	1.0	6 (−1–12)	65 (49–80)	0.09
Estrone (XLV)	1.0	−2 (−8–5)	65 (49–80)	−0.03
Equilen (CLVI)	1.0	4 (3–5)	86 (80–92)	0.05
		Miscellaneous		
Cholesterol (XIII)	1.0	16 (4–27)	75 (49–100)	0.21
Pregnane-3α 20α-diol (XCV)	1.0	−8 (−5–−10)	70 (49–92)	−0.11
21 Chloroprogesterone (CLXI)	1.0	6 (−12–92)	93 (83–100)	0.07
Δ^4 Pregnene 17α 20α diol-3-one (CCV)	1.0	20	92	0.22
20 21 Epoxy Δ^4 pregnen-3-one (CLXII)	1.0	12 (11–13)	79 (77–80)	0.15
Sodium cholesterol sulfate (CLX)	1.0	3 (2–8)	72 (64–80)	0.04
	2.0	18	64	0.28

Choline acetylase

Torda and Wolff [5] have studied the influence of steroids on the synthesis of acetylcholine by minced frog brain Cholesterol (XIII) had no in vitro influence but testosterone (VIII) dehydroepiandrosterone (XXIII) methyltestosterone (XCVI) and Δ^4 androstene 3 17 dione (LXI) depressed the synthesis

Miscellaneous

Dirscherl and Knuchel [80] have reported the activation of enolase hexokinase and carboxylase by androgens and estrogens Opsahl [90] has described the in vitro inhibition of hyaluronidase by adrenocortical steroids Other biologically active steroids such as progesterone (XCIV) and testosterone (VIII) were practically without influence Kalman [134] inhibited both the malic dehydrogenase and succinoxidase systems in a rat liver homogenate preparation by the addition of the sulfate esters of androsterone (XXV) and testosterone (VIII) and testosterone 17β β diethylaminoethyl carbonate hydrochloric acid (CCXIX)

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PART FOUR

Clinical Aspects

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CHAPTER

15

Normal Puberal Development in Boys

The schedule of development of the sex organs and secondary sex characteristics and the wide variation in age of onset of this process must be fully appreciated by the clinician before he attempts to evaluate the young boy who is allegedly retarded The stimulus which initiates puberal development possibly has its origin in a neurohypophyseal *mechanism by which the hypothalamus stimulates the anterior pituitary* to secrete increasing quantities of gonadotropin The type of pathway through which the hypothalamus might act upon the pituitary is far from being clarified Gonadotropin (chiefly luteinizing *hormone*) promotes growth of the Leydig cells of the testis which in turn secrete androgen Androgen operating in conjunction with follicle stimulating hormone brings about maturation of the tubules and active spermatogenesis It is testicular androgen of course which is *responsible* for the development of male secondary sex characteristics

Another important determinant which probably operates to control the schedule of development of sex structures is the sensitivity of these organs to the hormone which stimulates them as affected by chronological age Hooker found that rats castrated at birth showed during the puberal age period a seminal vesicle response with doses of testosterone (VIII) one fifth as great as those required either before or after this time[1] In other words end organ responsiveness was at its peak at the age when puberty would have been expected to occur

From the age of 11 to 18 or 19 there is a fairly systematic schedule for the maturation of the testes and secondary sex structures The start of this development process marks the beginning of pubescence or puberty The term puberty is reserved by some to denote a specific point of transition when the sex organs first become functional or more specifically the time at which procreation becomes possible Erectile function of the penis is actually present shortly after birth and ability for intercourse with orgasm antedates by some time the

Testes and scrotum

As might be anticipated the first organ to participate in puberal development is the testis. Almost stationary in growth for the first 10 years of life the testis undergoes an abrupt increase in size between the ages of 11 and 13 whereupon growth progresses rapidly for the next 5 or 6 years (Table 1). Leydig cells which had been present

TABLE 1

AVERAGE SIZE OF MALE GENITALIA FROM BIRTH TO MATURITY[55]

Age (years)	Testis		Penis		
	Length (cm)	Volume (cc)	Circumference Relaxed (cm)	Length Relaxed (cm)	Length Stretched or Erect (cm)
Under 1	1 5	0 6	4 0		4 0
1–2	1 6	0 7	4 0		4 [illegible]
3–4	1 6	0 8	4 0	3	5 5
5–6	1 6	0 8	4 5		6 0
7–8	1 6	0 8	4 5	3–4	6 0
9–10	1 6	0 9	4 5	3–4	6 0
11	1 7	1 5	4 5		6 5
12	1 9	2	[illegible] 0	3–7	7 0
13	2 3	5	6 0		9 0
14	2 8	8	7 0		10 0
15	3 0	1[illegible]	[illegible]		1[illegible] 0
16	3 5	13	8 0		12 5
17		15	8 5		13 0
18–19		16	8 5		13 0
Over 19	4–5	1[illegible] 5	8 5	6–10	13 0

in utero but disappear shortly after birth reappear again at 11 to 13 years. Meanwhile the Sertoli cells undergo differentiation and spermatogonia increase in number. Soon thereafter spermatogenesis is instituted by the progressive development of spermatocytes, spermatids and spermatozoa. By the age of 15 spermatogenic function is usually well established. In studies of a group of boys ranging from 9 to 17 years of age spermatozoa were occasionally observed in samples of morning urine from boys as young as 11. Of 24 subjects

attainment of spermatogenic function The term adolescence usually refers to the age interval after procreative powers have been attained but during which a continued growth of sex structures occurs until the final adult status is reached The terms pubescence puberty and adolescence are often used rather loosely or interchangeably and with variable meaning In this chapter the entire process of maturation from its inception to completion will be referred to as puberal development

Time and Sequence of Development of Puberal Changes

Although wide variations among individuals are encountered and will be commented upon later it will be worth while first to consider

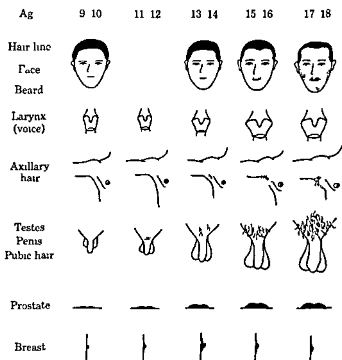


Fig 1 Average timing of developmental changes in sex structures (Modified from Schonfeld)

the timing of puberal development in the average boy This schedule is illustrated schematically in Fig 1 The reader is referred to the papers of Greulich et al [3] Schonfeld [4] Kubitschek [6] Wilkins [7] and Jung [8] for the original data and source material It will be of interest to consider the separate organs in detail

tween the ages of 12 and 15 a spurt in growth brings the rate to about 3 inches per year for the over all average[10, 11] Some boys may for a time greatly exceed this rate A rapid increase in weight due largely to growth of muscle tissue parallels the rapid advance in height After the age of 15 growth rate slows very rapidly and beyond the eighteenth year very little further increment in stature may be ex pected The puberal spurt in growth is considered to be due to the somatic effect of androgen which includes stimulation of growth at epiphyseal centers (and eventual closing) along with an anabolic effect on tissues in general Estrogen which is produced in increas ing amounts at this age may participate in the somatic stimulation

Hair growth

The development of sex hair involves a transition of the fine down hair to fibers which are thicker longer more deeply pigmented and which possess a medulla

Hair in the pubic region at the base of the penis is the first to re spond In the beginning it is rather short and straight but over a period of months the hair grows longer becomes curly and spreads out to form first a horizontal type of escutcheon and within several years usually a typical diamond shaped male pattern (Fig 1) Axil lary hair growth follows within a year after the appearance of pubic hair and after an additional year (age 14 to 15) there is usually a visible fuzz on the upper lip and below the ears along with some lengthening of the hair on the forearms and then the legs However by 16 or 17 years half of the boys have not yet shaved and the others require shaving only one to four times a month

By the age of 15 the frontal hair line which in the juvenile state was an uninterrupted curve has begun to acquire wedge shaped indentations at the lateral margins characteristic of the adult male

Although most puberal changes are essentially complete by 18 or 19 years hair development is an exception Often the beard continues to increase in rate of growth and coarseness even after the age of 20 Chest hair may not appear until after this time and the scapular region is usually not covered until middle life Likewise areas over the external ear the eyebrows and the nares do not reach their peak until late middle life or old age The frontal hair line also frequently continues to recede in the well known manner until a variable degree of baldness is acquired

The extent of body hair growth and also the ultimate degree of bald ness are determined largely by the genetic constitution of the individ ual although their complete development is impossible without an

who showed positive specimens 23 had already developed pubic hair but in only 18 was axillary hair present

Because the testis is the first organ to participate in puberal development serial measurements of testicular length at 6 month intervals are helpful in the evaluation of cases of delayed development in which the problem is to predict whether normal sex maturation will be achieved spontaneously

Scrotal enlargement which accompanies testicular growth is promoted by the androgen being elaborated by the developing Leydig cells The sack becomes more elongated pendulant and relatively more narrow at its proximal attachment

Penis and prostate

A detectable increase in penile length and breadth may usually be noted by the age of 12 shortly after testicular growth has started It is a striking fact that although a clinical assessment of gonadal development usually depends upon an impression of penile length there is a remarkable paucity of statistical data on this simple measurement This may be ascribed largely to the unwillingness of a meticulous investigator to trust such measurements The length of the relaxed penis is greatly affected by thermal tactile, and emotional stimuli Measurements on the erect or stretched penis as have been made by Schonfeld[5] (Table 1) are subject to less error because the organ is then at or near its maximum attainable length A thick pubic fat pad may literally envelop the penis of an obese boy All measurements therefore should be made from the underlying pubic bone

In many infants and young children the glans and prepuce are at least in part adherent Such a state may persist particularly in the coronal area until the onset of puberal development when there is a spontaneous separation of the entire foreskin

A palpable thickening of the prostate is usually discernible at the same time that the penis begins to grow The other accessory glands along with the prostate continue to enlarge over a period of 4 to 5 years Secretory activity as evidenced by the presence of at least small quantities of ejaculate at the time of orgasm is usually apparent by the fourteenth year The insensible oozing of prostatic fluid into the urethra begins at about this time and causes the sharp rise in urinary acid phosphatase[18]

Body growth

Growth rate in the average boy from the age of 5 to the age of 12 is relatively slow and fairly constant at about 2 inches per year Be

the hair and the eye color The genital and perianal regions being more conspicuously affected than other parts of the body become very much darker than the surrounding skin

Breasts

Breast enlargement is seen in the majority of boys at some time during puberal development The swelling is usually subareolar but may extend beyond this limit and may sometimes be easily visualized The enlargement takes the form of a firm well defined flattened somewhat tender and movable mass It tends to reach its peak between the fourteenth and fifteenth year and then usually recedes after 12 to 18 months although in some cases the tissue persists into adult life Of 150 consecutive white draftees whose sexual development was normal and whose ages ranged from 18 to 35 (mean age 25) 15 per cent had palpable subareolar masses which were usually 1 5 to 2 cm in diameter[3] Those who remembered the date of onset placed it usually at the age of 14 to 15 Twenty nine per cent of a similar group of colored men showed the same type of enlargement Of 1000 consecutive white draftees observed for *visible* breast enlargement (not due to fat) 0 7 per cent exhibited such a finding as compared to 2 per cent of 200 colored men

Although estrogen excretion is increasing throughout puberty and may play a part in breast growth at this time it is quite possible that the puberal stimulation of this organ is actually due to androgen A similar effect is often encountered in eunuchoid men shortly after testosterone therapy is started

Sex drive and behavior

Although the anatomical events of puberty represent a phase of development which is rather sharply delimited psychosexual development even though accelerated at puberty is a very gradual process which begins well before sexual maturity and continues for many years afterward Sexual behavior in relation to age has been extensively studied by Kinsey[6]

During infancy and early childhood erectile function is present and penile erections may be a daily occurrence Erections at this age may be completely spontaneous and the stimuli which produce them can not be consistently classed as erotic It is however of interest that strong emotional attachments to individual girls along with a desire for physical contact may be manifested in the early grade school period and the emotional pattern may be quite similar to that of amorous attachments of mature life At its beginning nevertheless

adequate supply of male hormone The progressive change in hair growth during later years of adulthood is not due to a continuation of the puberal rise in androgen secretion but is probably traceable to factors within the hair follicle which come more and more into prominence as age advances The same explanation could apply to the increased facial hair seen in some women later in life

Voice change

Voice change is due to enlargement of the larynx with thickening and lengthening of the vocal cords After an initial huskiness and a transitional period during which the vocal uncertainty reflects an attempt to adjust to a new voice range the pitch becomes fixed at a lower level A further deepening then may continue for several years

Glands of the skin

The secretory activity of the axillary glands is augmented even before hair growth is under way in this area The secretion is composed of the products of both the ordinary sweat glands (merocrine) and the apocrine glands It is the latter which are responsible for the characteristic odor of this region in the adult

Activity of the sebaceous glands of the skin is profoundly altered by androgenic hormone [1] Oiliness increases particularly on the face and the sebaceous ducts plugged with secretion form comedones and pustular acne of varying severity Some degree of acne is demonstrable in 99 per cent of boys at one time or another between the ages of 13 and 20 The peak incidence is at 18 and thereafter a gradual improvement is to be expected The predisposition to acne is of course dependent on an intrinsic susceptibility of the skin itself although the presence of androgen is a conditional requirement

The product of the oil glands of the scalp undergoes an interesting transformation at puberty Short chained odd numbered fatty acids make their appearance in substantial amount at this time and are believed to be responsible for the well known postpuberal resistance to ringworm infections of the scalp [13]

Pigmentation

Skin pigmentation especially as manifested in the tanning effect of ultraviolet light is intensified by androgen [14] It is therefore not surprising that the shade of a boys complexion ordinarily becomes darker after puberty The deepening of pigmentation also involves

these values in boys rise to the higher adult male level (see also Chapter 13)

The Variability of Puberal Development

There are wide differences in the time of onset of puberal development and equally wide variations in the size attained by the genital organs the extent of the sex hair growth depth of voice etc These features are genetically determined and although their mature status cannot be attained without androgen it does not follow that a high degree of development indicates a superior output of androgen by the testis In other words a very hirsute man is no more masculine in an endocrine sense than is one with a minimal growth of chest hair nor does a tenor voice indicate a low level of androgen secretion

Boys with an asthenic habitus show some tendency to mature at a later age than average whereas those of pyknic habitus often tend to develop earlier than the average[6] A correlation between personality type and time of puberal development has not been demonstrated

The observations of Schonfeld[5] are the basis for the data in Table 2 This compilation is concerned with the range of variation in

TABLE 2

RANGE OF VARIATION OF TESTIS VOLUME AND LENGTH OF STRETCHED (OR ERECT) PENIS

Age (years)	Penis Length (Stretched) (cm)	Testis Volume (cc)
Birth	[illegible] 8	0 3 2
1-2	3-8	0 3-2
3-4	3-8	0 3-2
5-6	4-[illegible]	0 3-[illegible]
7-10	4 10	0 3 5
11	4 10	0 5-11
12	4 14	0 8 17
13	4-15	1 [illegible]
14	4-16	1 3 27
15	6-17	2 0-27
16	5-18	[illegible]
17-25	9-20	7-33

Compiled from the observations of Schonfeld[5] on a group of 1500 normal boys

the age of onset and in the completion of puberal development Table 3 likewise is derived from Schonfeld's work and is based on observations of the variation in genital size of a large series of normal

such an emotion may be entirely devoid of any desire for actual sexual contact Sex play involving observation and handling of their genitals or those of playmates—either girls or boys—is common in childhood but here again even though there is a unique emotional reaction to genital organs in general the motivation may involve little or nothing of an erotic nature A neuromuscular response identical with orgasm is also possible in very early life produced either by genital manipulation or more commonly by certain physical activity notably by climbing a pole or a rope Any desire for participation with another person for the incitement of orgasm is by no means the rule

The rate at which all the physiological emotional and genital manifestations of sex drive and sex expression become fused into the usual adult patterns depends partly on the social conditioning of the child It is quite obvious nevertheless that the entire process is greatly accelerated during the puberal years The incidence of masturbation for example rises from 2 per cent at age 10 to over 80 per cent by age 15[16] A similar sharp rise is noted for all forms of sexual outlet whether erotic dreams with orgasm homosexual activity or heterosexual intercourse The awakening of sex interest and the rapid acceleration of sex activity during the puberal years correlate very nicely with the increased androgen secretion by the testes at this time and most likely are due in part to increasing levels of this hormone The slow onset of definitive sex interest and the low level of indulgence in girls along with observations on the stimulating effect of androgen in some women (Chapter 18) accord with such an interpretation One cannot conclude however that androgen is the sole determinant of sex desire and its frequency of expression even though it may be a prime factor

Miscellaneous changes

Lymphoid tissue steadily increases in mass during early childhood until a maximum is reached just before puberty After this time under the dominance of sex hormones during puberty such organs as the thymus tonsils adenoids and lymph nodes rapidly decrease in size until by age 16 they are reduced to near adult proportions

Although in girls the thyroid is commonly seen to enlarge at puberty particularly if iodine intake is deficient such enlargement is rarely encountered in boys The progressive decline of basal oxygen consumption from childhood to late life is slowed during early puberal development and accelerated in adolescence

During childhood there is no sex difference in the red cell and hemoglobin content of the blood Between the ages of 14 and 17

androgen as noted below One of the disorders to be ruled out in such cases is gross adrenal hyperfunction due to tumor or hyperplasia In such an instance there is regularly an excretion of 17 ketosteroids far in excess of that expected for the chronological age

If the testes remain infantile well beyond the age of expected onset of puberal development and pubic hair growth takes place without the participation of other male secondary sex structures it is fair to conclude that testicular maturation is retarded Although this may be a normal variation nevertheless one should suspect hypogonadism when such a reversal of sequence is encountered after the age of 15

Hormone A says

Androgens and 17 ketosteroids

The excretion of androgens and 17 ketosteroids in relation to age is considered in some detail in Chapter 20 It is enough to say at this point that the urinary concentrations of androgens and related compounds are at low levels until about the age of 7 when there is a fairly sharp increase in both sexes which is maintained until toward the end of puberty Beyond this time there is a much slower increase with advancing age until sometime beyond the age of 20 It is unlikely for several reasons that the rise in boys at age 7 can be accounted for by the awakening of testicular function Neither the testes nor secondary sex structures show any acceleration in growth until 4 or 5 years later Moreover a similar increase in the excretion of these compounds is noted at about the same age in girls This may reflect an increased secretion of androgens and related steroids by the adrenal cortex rather than by the gonad After puberal maturation is under way the excretion of 17 ketosteroids and androgens rises more sharply in boys than in girls This divergence is most certainly traceable to the contribution of the testicle

Estrogens

Estrogens are detectable in the urine very early in life but remain below 10 I U per 24 hours until the age of seven [17] There is then a steady rise to 30 or 40 I U by the age of 15 to 17 In boys there is only a slight additional increment during the succeeding 5 to 10 years Girls on the other hand show a marked rise at about the age of 11 after which time the levels not only remain much higher than those of boys but also assume a cyclic variation as a consequence of the appearance of rhythmic ovarian activity with attendant intermenstrual peaks of estrogen secretion

white boys from birth to sexual maturity. The difference between the extreme high and low measurements is very striking both during childhood and after maturity. It behooves the physician to recognize these normal variations so that he will not attach false significance to so-called infantile genitalia in a 10-year-old boy or attempt to judge testicular hormone production in the adult by genital size alone. It may be noted in Table 1 that the most extreme variations

TABLE 3

VARIATION OF TIME OF PUBERAL DEVELOPMENT

Age	Per Cent Having Started	Per Cent with Essentially Complete Development
1	0	0
5	0	0
9	0	0
10	4	0
11	24	0
12	56	0
13	85	0
14	94	0
15	100	7
16	100	20
17	100	51
18	100	63
19	100	74
21	100	83
25	100	100

Based on observation of Schonfeld on a group of 1475 normal boys

within a given age group occur near the age of puberty. This of course is simply a reflection of the high variability in age of onset of sexual development.

In general the sequence of participation of various organs is identical no matter whether the onset of the process as a whole begins early or late. Occasional exceptions are encountered, as in instances where pubic hair begins to grow (presumably in response to adrenal androgen) before the testes and penis have shown any change. A premature growth of pubic hair prior to the age of 11 or 12, before the testicles have started to develop, may be a normal occurrence due either to a precocious sensitivity of the pubic hair follicle to the existing normal level of adrenal androgen or to an unusually early "adrenarche," that is, an accelerated timing of the prepuberal rise in adrenal

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Gonadotropins

The impetus to puberal sex development is assumed to be mediated by the anterior pituitary gland It is therefore significant that neither Catchpole nor Nathanson s group[17] could detect gonadotropin in the urine of young boys until after the age of 11 From the age of 12 through adolescence there was a gradual increase from an initial two to four units per day to levels more near the adult range It should be borne in mind that the methods of gonadotropin separation which were employed in these studies give lower recoveries than some of the more recent methods and therefore will not detect very small quantities Catchpole s normal range for adult males was 7 to 20 mouse uterine units per day Such values are low when compared with those obtained by the alcohol precipitation dialysis method which gives recoveries approximately twice as great There is therefore as yet no strong evidence that gonadotropin is totally absent from the urine before puberty It is quite possible that the hormone may be present in early life but not at a level detectable by methods which have been used That a rise occurs during puberal development cannot be denied

Assays of urinary gonadotropin afford little specific help in predicting the imminence of sex maturation in boys The patient s own testes are as good an indicator of the level of circulating gonadotropin as are the genital organs of the mouse which receives a test dose of urinary extract Thus perceptible testicular growth in the subject is demonstrable at the same age that gonadotropin excretion begins to rise A high level of excretion on the other hand if associated with persistently small testes would denote refractoriness of the testicles due to a primary intrinsic defect (Chapter 17)

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physeal centers (advanced bone age) If the condition is not promptly corrected premature epiphyseal closure leads to a stature which is shorter than average Neither mental age nor the schedule for the eruption of permanent teeth is characteristically affected Psychosexual precocity as manifested by awakened sex interest and aggressiveness is not the general rule[1] but has been seen perhaps most often in Leydig cell tumors of the testis In the first few months of life due to an apparent insensitivity of even such responsive end organs as the penis and pubic hair the presence of androgen excess may not be clinically apparent There is a delay in their development until the *age of 6 months to 3 years*

Although sex precocity in general is sometimes loosely designated as "premature puberty" the term should be reserved for a special type of true precocious puberty in which along with the secondary sex changes normal testicular development also occurs This condition

TABLE 1

CAUSES OF MALE SEX PRECOCITY*

Complete genital precocity true precocious puberty	Idiopathic †		55%
	Cerebral	Pineal neoplasm	18%
		Hypothalamic disease	13%
Incomplete genital precocity precocious pseudopuberty dissociated virilization (testes do not mature)	Adrenal cortical lesion		10%
	Interstitial cell tumor of testis		4%

* From a series of 176 cases compiled by Seckel

† In most of these cases a pathologic lesion was not completely excluded by operation biopsy or necropsy however the longevity of the patients argues against the presence of tumor

TABLE 2

CAUSES OF ANDROGEN EXCESS DUE TO ADRENAL LESIONS IN PREPUBERAL BOYS (BEFORE AGE 10)

Nature of Adrenal Lesion	Onset of Lesion	Clinical Syndrome	Per Cent of Total Cases	Frequency in Boys as Compared to Girls
Hyperplasia	Prenatal	Precocious pseudopuberty mixed adrenal disease	55	1/5
Hyperplasia	Postnatal	Precocious pseudopuberty	None reported	
Tumor	Postnatal	Precocious pseudopuberty	31	1/[illegible]
Hyperplasia	Postnatal	Predominantly Cushing's syndrome	None reported	
Tumor	Postnatal	Predominantly Cushing's syndrome	14	1/5

Adapted from the data of Wilkins* ([illegible]9 reported cases)

CHAPTER

16

Conditions of Androgen Excess

General Clinical Manifestations

Certain manifestations common to all disorders of androgen excess will be reviewed before the various clinical entities are considered in detail The general pattern is similar irrespective of the site of the lesion although individual variables such as sex and age modify the picture in various aspects In the preliminary discussion which follows it is assumed (1) that the androgen excess is in relatively "pure" form that is not complicated by concomitant corticoid or estrogen excess and (2) that the degree of overproduction ranges from moderate to severe Disorders characterized by mixtures of hormonal effects or attended by minimal hypersecretion of androgen will be discussed as separate entities

Prepuberal boys ("isosexual sex precocity")

Excessive production of androgen in the prepuberal boy irrespective of the source of hormone leads to precocious growth and maturation of secondary male sex structures along with a spurt in statural and muscular growth Because both the sex structures and the somatic tissues share in the precocity the condition is sometimes termed macrogenitosomia or "Infant Hercules At the onset the penis is the first secondary sex organ to be affected It often grows to adult proportions and also assumes the dark hue characteristic of sexual maturity Erections may become frequent The scrotum darkens and becomes pendulous pubic hair begins to grow the prostate enlarges and as at puberty acne may develop If the condition persists for a number of months or years axillary hair appears the voice deepens facial hair lengthens and a powerful musculature becomes quite striking A spurt in statural growth is characteristic Accompanying the increase in bone length is an acceleration of maturation of the epi

Postpuberal women

Hirsutism is one of the earliest and most prominent symptoms of androgen excess in mature women The pubic hair pattern becomes masculine and an excessive coarse growth is evident not only over the face but also over the extremities and chest In cases of moderate or severe androgen excess the clitoris grows larger the voice



Fig 1 Baldness in a 48 year-old woman with a lipoid cell masculinizing tumor of the ovary The photograph on the right was taken one year after removal of the tumor Regrowth of hair is complete (Case of Douglass [6] courtesy of C V Mosby Co)

deepens and body musculature becomes prominent Acne may appear or if pre existing may be intensified Baldness similar to that seen normally in men is not infrequent (Fig 1) A process of defeminization also is apparent The breasts shrink in size and the body and face become angular because of a decrease in subcutaneous fat in relation to the underlying bone and the thickened musculature Menses decrease in frequency and usually cease entirely in the course of time Ovulation ceases and the uterus becomes atrophic

Postpuberal men

Pure androgen excess in a normal man is not attended by clinically recognizable manifestations An increase in 17 ketosteroid excretion and a depression of spermatogenesis would be anticipated

is sometimes termed "complete genital precocity." The various primary causes of androgen excess in the young boy will be discussed under separate sections. The relative incidences of the four disorders which are responsible for male sex precocity are summarized in Table 1. A further classification of the several types of adrenal cortical disorders is tabulated in Table 2.

Prepuberal girls ("heterosexual sex precocity")

Excessive androgen production in a young girl is always traceable to a disorder of the adrenal cortex. The nature of the various types of adrenal hyperfunction will be discussed under separate headings, as will the causes and consequences of its inception prior to birth. A tabulation of the causes and of the types of virilizing syndromes in girls occurring before the age of 10 is presented in Table 3.

TABLE 3

CAUSES OF ANDROGEN EXCESS IN PREPUBERAL GIRLS (BEFORE AGE 10) *

Nature of Adrenal Lesion	Onset of Lesion	Clinical Syndrome	Per Cent of Total Cases	Frequency in Girls as Compared to Boys
Hyperplasia	Prenatal	Pseudohermaphroditism, virilism (mixed adrenal disease)	69	3×
Hyperplasia	Postnatal	Virilism	None reported	
Tumor	Postnatal	Virilism	14	2×
Hyperplasia	Postnatal	Primarily Cushing's syndrome	None reported †	
Tumor	Postnatal	Primarily Cushing's syndrome	17	5×

* Adapted from the data of Wilkins[3] (121 reported cases).
† Since Wilkins' review, a case of hyperplasia has been reported in an 8-year-old girl.[95] See also Fig. 7.

The clitoris, being the female counterpart of the penis, is enlarged in prepuberal virilism, and pubic hair ultimately appears. As the duration of the disorder lengthens, the voice deepens, axillary hair develops, the muscles become more prominent, and acne may occur. Probably owing to poor reactivity of target organs during infancy and early childhood, facial and body hair are seldom conspicuous, but in the older child hirsutism is an increasingly prominent feature. As in boys, statural growth is excessive for the chronological age, and epiphyseal development is shown by x-ray to be prematurely advanced. Psychosexual, mental, and dental development are not characteristically affected.

Treatment is by removal of the involved testis There are no instances of malignancy as proved by metastasis in the fourteen cases reported in children

At operation the cut section of the tumor is seen to be brown in color *owing to the presence of an unidentified pigment* perhaps a lipochrome The outline is sharply circumscribed but a well developed capsule is lacking Microscopically the cells are disposed either in sheets or in cords Like normal Leydig cells their morphology is not constant They vary in outline from oval to polygonal and the cell boundaries are usually but not invariably sharply defined Cytoplasm is characteristically abundant and is pink staining At times it is homogeneous and again may be spongy or vacuolated owing to the presence of lipid The nuclei are likely to be of moderate absolute size are circular or ovoid and possess a prominent nucleolus Chromatin is variable in density and is dispersed in vacuolar or granular arrangement Tubules of the surrounding normal testicular tissue may exhibit some degree of maturation short of actual sperm formation

Over forty cases of Leydig cell tumor have been reported in adult men The condition is diagnosed with certainty only by the histological characteristics of the tumor although one might predict the nature of such a tumor before its removal if 17 ketosteroids were found to be high and urinary chorionic gonadotropin absent Gynecomastia may occasionally occur This would suggest that in addition to androgen estrogen may be elaborated by the tumor The proportion of tumors which are malignant is significantly higher in mature men than in children being encountered in 20 to 25 per cent of the cases

Ovary

ARRHENOBLASTOMA Well over one hundred cases of arrhenoblastoma have been reported in the literature The most recent extensive review is by Iverson[8] These tumors are most commonly seen between the ages of 20 and 40 but have occurred as early as age 14 and as late as age 66 Virilization and amenorrhea are the most frequent early manifestations Masculinization tends to be rather severe and is usually characterized not only by hirsutism but also by distinct clitoral enlargement shrinkage of the breasts deepening of the voice and a transition of body contour from feminine to masculine The excretion of 17 ketosteroids is usually normal but occasionally is moderately increased The fact that these urinary metabolites are not strikingly elevated suggests that the tumor elaborates a highly potent androgen which gives rise to relatively small quantities of urinary

Very few studies of this nature have been made in cases of testicular or adrenal tumors which before their surgical removal might have secreted excessive quantities of androgen

Reversibility of anatomic and functional changes

In the adult female when the source of excessive androgen is removed or suppressed the menstrual function and fertility are promptly restored the breasts regain their normal dimensions the excessive musculature shrinks and the feminine distribution of body fat reappears The clitoris tends to decrease in size over a period of months but may remain distinctly large The voice may or may not lose its deep pitch depending on the length and severity of the disorder before treatment Excessive hair tends to decrease but may require many months or years before it is lost completely or may never entirely disappear

In the prepuberal child an enlarged penis or clitoris tends to regress after excess hormone production is abolished but shrinkage is usually incomplete Pubic hair behaves similarly Frequency of erection in the male child decreases and excessive muscular development diminishes If epiphyseal closure has occurred the stunting in stature is irreversible

Disorders of Specific Organs

Testis

LEYDIG CELL (INTERSTITIAL CELL) TUMOR Leydig cell tumors are comparatively rare Twelve cases which had been reported up to 1952 are summarized in articles by Newns[4] Melicow[5] and Fraser[6] Two additional cases have been reported more recently

The presence of the tumor is heralded by sex precocity which usually makes its appearance between the ages of 4 and 6 rarely as early as 2 The excretion of 17 ketosteroids is substantially increased (Chapter 20) The Friedman test for chorionic gonadotropin is negative Palpation of the testes reveals one of them to be of the normal small size characteristic of the prepuberal state whereas the involved gland is relatively large The degree of enlargement varies with the duration of the lesion A testis the seat of a tumor less than 1 cm in diameter may exceed the normal member of the pair in size by a very scant margin whereas advanced tumors may attain a weight of several hundred grams and exceed 10 cm in length The smaller tumors are frequently buried within the interior of the gland and do not distort the surface

existence of mixed tumors (*gynandroblastoma*) which contain elements resembling both arrhenoblastoma and granulosa cell tumor is consistent with such a theory Of interest is the case of Kershner et al[13] in which a masculinizing tumor was called arrhenoblastoma by one group of consultant pathologists and granulosa cell tumor by another Another theory of origin is that the arrhenoblastoma is a teratomatous variant A variety of tissues such as bone cartilage and mucous membrane have been found in a certain proportion of cases[14]

The arrhenoblastoma is frequently malignant although it metastasizes slowly The known incidence of malignancy as proved by metastasis is 20 per cent[15] The malignant type is usually recognizable by its gross extension at the time of initial exploration The histologic morphology of the tumor is not in itself a reliable guide in prognosis In women of the child bearing age who desire subsequent pregnancies surgery is commonly restricted to removal of the involved ovary and accompanying tube unless malignant invasion is evident at laparotomy In postmenopausal women it is preferable to remove all pelvic sex organs as a routine precautionary measure

VIRILIZING LIPOID CELL TUMORS (MASCULINOVOBLASTOMA) Included in this category are tumors variously termed "adrenal cortical cell" *luteoma* " and "hypernephroma of the ovary " Because of the controversy as to whether these tumors can be assigned to separate subgroups on the basis of morphology histochemical characteristics clinical manifestations or urinary assays they will be discussed as a single type It is uncertain whether some are derived from primitive adrenal remnants others from lutein or theca lutein cells still others from primitive male directed inclusions or whether perhaps all originate from but one of these sources Their masculinizing characteristics suggest that androgen or an androgen precursor is elaborated by the tumors but this is of no aid in clarifying their histogenesis Ovary testis and adrenal cortex all are capable of manufacturing such steroids

Telium [9] groups the lipoid cell tumors with arrhenoblastomata and favors an origin from an embryonic testis remnant which has differentiated to form functional Leydig like cells Iverson[8] also classifies these tumors as variants of arrhenoblastoma but construes the whole class as being derived from ovarian mesenchyme rather than male directed tissue The lipoid cells would represent the neoplastic equivalent of theca lutein cells Shippel's views are similar[2] An experimental finding in accord with such a theory is the production of lutein like tumors in the ovaries of mice subjected to x ray irradiation[16, 17] The attendant masculinization in these mice along with such features as

metabolites Classical Cushing s syndrome is not produced by this tumor although some cases have been encountered with diabetic glucose tolerance curves and an elevation of the red count

The neoplasm is almost always unilateral It may occasionally be too small to recognize on pelvic examination but is usually palpable and averages 12 to 15 cm in diameter Multilocular cysts occasionally develop and may grow to such dimensions as to fill the lower abdomen On section the tumor characteristically appears lobulated within a well defined capsule The color ranges from gray to yellow and may vary from one region to another Necrosis is frequent and areas of hemorrhage often are conspicuous

Histologically several different types of tissue may be present All types are frequently encountered in the same tumor but in other instances a single variety may predominate Meyer s classification[9] of the morphological types is still in common use The most highly differentiated variety is composed of simple tubular structures postulated by Meyer to be the counterpart of testicular tubules The most undifferentiated type contains solid masses of spindle cells with large nuclei which strongly resemble sarcoma An intermediate variety possesses cells with prominent nuclei which in some areas are arranged in circles resembling tubular structures but elsewhere are disposed in irregular or anastomosing columns reminiscent of embryonic sex cords The latter two varieties of tissue in particular are interspersed with variable numbers of polyhedral or rounded cells with rather abundant pink staining cytoplasm Although it has been proposed that the latter cells are the neoplastic equivalent of testicular Leydig cells their abundance is not necessarily correlated with the severity of masculinization It is also of interest that the intermediate and sarcoma like neoplasms almost invariably lead to virilization whereas the highly differentiated tubular types most often do not

The term arrhenoblastoma was coined by Meyer The name not only indicates that the neoplasm causes virilization but also implies that it is derived from persistent embryonic male elements within the ovary Although this concept of histogenesis is the classical one and is favored by Telium[10] serious dissent has been expressed by some who have studied the problem Norris[11] Shippel[12] and Iverson[8] believe that the tumors originate from primitive sex gland structures or ovarian mesenchyme which is not necessarily male directed They suggest that the tubular elements may be derived from indifferent sex cords Iverson proposes that the Leydig like cells are more likely related to ovarian theca lutein cells and that all three types of tissue can be formed from female directed components of the ovary The

existence of mixed tumors (gynandroblastoma) which contain elements resembling both arrhenoblastoma and granulosa cell tumor is consistent with such a theory. Of interest is the case of Kershner et al[13] in which a masculinizing tumor was called arrhenoblastoma by one group of consultant pathologists and granulosa cell tumor by another. Another theory of origin is that the arrhenoblastoma is a teratomatous variant. A variety of tissues such as bone, cartilage and mucous membrane have been found in a certain proportion of cases[14]

The arrhenoblastoma is frequently malignant although it metastasizes slowly. The known incidence of malignancy as proved by metastasis is 20 per cent[15]. The malignant type is usually recognizable by its gross extension at the time of initial exploration. The histologic morphology of the tumor is not in itself a reliable guide in prognosis. In women of the child bearing age who desire subsequent pregnancies surgery is commonly restricted to removal of the involved ovary and accompanying tube unless malignant invasion is evident at laparotomy. In postmenopausal women it is preferable to remove all pelvic sex organs as a routine precautionary measure.

VIRILIZING LIPOID CELL TUMORS (MASCULINOVOBLASTOMA) Included in this category are tumors variously termed "adrenal cortical cell luteoma" and "hypernephroma of the ovary". Because of the controversy as to whether these tumors can be assigned to separate subgroups on the basis of morphology, histochemical characteristics, clinical manifestations or urinary assays, they will be discussed as a single type. It is uncertain whether some are derived from primitive adrenal remnants, others from lutein or theca lutein cells, still others from primitive male directed inclusions, or whether perhaps all originate from but one of these sources. Their masculinizing characteristics suggest that androgen or an androgen precursor is elaborated by the tumors, but this is of no aid in clarifying their histogenesis. Ovary, testis and adrenal cortex all are capable of manufacturing such steroids.

Telium[10] groups the lipoid cell tumors with arrhenoblastomata and favors an origin from an embryonic testis remnant which has differentiated to form functional Leydig like cells. Iverson[8] also classifies these tumors as variants of arrhenoblastoma but construes the whole class as being derived from ovarian mesenchyme rather than male directed tissue. The lipoid cells would represent the neoplastic equivalent of theca lutein cells. Shippel's views are similar[1]. An experimental finding in accord with such a theory is the production of lutein like tumors in the ovaries of mice subjected to x ray irradiation[16,17]. The attendant masculinization in these mice along with such features as

obesity polycythemia and adrenal atrophy suggests that steroids with androgenic and cortin like activities are either secreted or derived from secreted precursors

That all or any of the lipoid cell tumors represent neoplasia of adrenal cortical rests seems difficult to substantiate on histological grounds alone Kepler[18] and Dockerty[14] have favored such a theory because of certain clinical manifestations resembling Cushing s syndrome in many cases It is true also that one case of malignant lipoid cell tumor subjected to laparotomy died postoperatively in collapse and the adrenal cortex was found to be atrophic at autopsy[19] This would suggest an extra adrenal elaboration of cortical hormone capable of producing a Cushing like syndrome Nevertheless the experimental findings in mice cited above are compatible with the notion that the source of such a hormone might be from some variety of ovarian cell rather than an adrenal rest The finding of Groat[0] that adrenalectomy of ground squirrels is followed by the development of tissue within the ovary which not only resembles the adrenal cortex but also maintains life does not prove that dormant adrenal tissue exists in the gonad Metaplasia of fibroblasts or hyperplasia of cells of the lutein family might ensue as a consequence of the hypersecretion of ACTH and perhaps other tropic hormones after adrenalectomy The steroid material manufactured by the ovarian cells may sufficiently resemble adrenal hormones to substitute for normal adrenal secretion A converse situation has been observed in certain strains of mice wherein ovariectomy is followed by adrenal cortical hypertrophy and feminization[21]

Virilizing lipoid cell tumors are relatively rare Merivale and Forman[2] cite the literature up to 1951 and add an additional case If previously reported cases are all acceptable examples of this tumor their case is number 37 It is impossible to estimate the incidence of nonmasculinizing varieties which because of an absence of clinical symptoms have escaped recognition

The virilizing phenomena the age of incidence and the general clinical manifestations are similar to those of arrhenoblastoma Although Cushing s syndrome in malignant form and with well marked stigmata of protein depletion is not to be expected varying degrees of polycythemia hypertension obesity and impaired glucose tolerance are by no means rare[18] Hyperostosis cranialis interna is possibly more frequent than in the normal population[3] A moderate elevation of urinary 17 ketosteroids and androgens is common but by no means a constant finding (Chapter 20) Estrogen excretion sometimes rises That progestational steroids may be formed by the tumor is suggested by the

reports of a secretory endometrium in two cases[24] and of an elevated pregnanediol output.[28] The latter however is not invariable[29]

The tumors vary in size from 1 5 to 20 cm and occasionally they are cystic Encapsulation is the rule and the color is yellow orange or brown Microscopically the neoplasm is composed of large pale polyhedral cells arranged in columns or clumps within a delicate well vascularized fibrous stroma (Fig 2) The pink staining cytoplasm is abundant and is usually foamy as a result of a considerable quantity of lipid Fuchsinophilic granules and glycogen are frequently demonstrable but not without exception Most of the tumors are benign however three instances of fatal metastasizing lesions[7, 8] and one locally malignant tumor[19] are on record

Surgical management is similar to that of arrhenoblastoma Kepler advised that intensive therapy with cortical hormone be employed because of the risk of postoperative collapse as seen in Cushing's syndrome following the removal of an adrenal tumor which has suppressed the remaining normal tissue It is of interest however that such therapy has not been instituted in most cases reported yet only one fatality due to postoperative collapse has so far been mentioned This patient had an inoperable malignant lesion which was not removed[19]

Leydig cell tumor (hilus cell sympathicotropic cell) Berger[30] in 1942 reported a case of masculinization in a 50 year old woman which was associated with the presence of a 0 5 cm mesovarian tumor composed of "sympathicotropic cells" These cells also known as hilus cells, are found in the normal ovary In Berger's previous studies which antedated his encounter with a masculinizing tumor it had been concluded that these ovarian cells are related to the testicular interstitial cells of Leydig Morphologically they resemble Leydig cells in all respects even in that they contain the characteristic crystalloids of Reinke The term sympathicotropic is derived from their close approximation to nonmyelinated nerves

Sternberg[31] has reviewed the problem of the hilus cell and has reported two cases of tumor with masculinization One was an 86 year old woman with a 1 cm tumor in each mesovarium the other a 64 year old patient with a similar tumor in the right ovary Two cases aged 41 and 50 with masculinization accompanied by hyperplasia of the hilus cells were described One other patient with tumor and two with hyperplasia were mentioned but not documented at the time of writing A case of tumor has been described by Waugh and associates[32] (age 46) and another by Sachs and Spiro[33] (age 47)



Fig 2 Virilizing lipoid cell tumor of the ovary The cells are disposed in clumps and strands and are fairly large Many of them have a clear cytoplasm (Case of Douglass [9])



Fig 2 (*continued*)

STEIN LEVENTHAL SYNDROME (MICROCYSTIC OR SCLEROCYSTIC OVARIES HYPERTHECOSIS OVARII) In 1935 Stein and Leventhal[34] observed that in a series of women complaining of amenorrhea and sterility characteristic cystic changes were observed in the ovaries Stein s[35] latest report includes a total of seventy five similar cases Although the syndrome is poorly understood and not clearly delineated in some respects that it is not a rare disorder is suggested by the published reports of a number of authors[36-41] The condition is discussed because of an associated masculinization which although usually mild is present in a fair proportion of cases

Medical advice is usually sought by patients between 18 and 30 years of age who complain of amenorrhea and if married sterility Although the rare patient never experiences a menarche the usual story is of several years of normal or somewhat irregular periods followed by a progressively decreasing frequency until finally amenorrhea persists for many months Although excessive uterine bleeding was not originally reported by Stein and Leventhal it is being mentioned in the literature with increasing frequency Menometrorrhagia may

alternate with amenorrhea Basal body temperature curves and vaginal smears disclose no evidence of ovulation Biopsies of the endometrium usually reveal a proliferative (estrogenic) or hyperplastic reaction A secretory phase is occasionally encountered but without evidence of recent ovulation at laparotomy

Half of the cases exhibit hirsutism of varying severity which may involve the face lower abdomen or much of the body In a smaller percentage of patients there is hypertrophy of the clitoris Deepening of the voice is rare and loss of feminine body contour severe atrophy of the breasts baldness or excessive muscular development are not to be anticipated Approximately a fourth of the cases are somewhat obese

On pelvic examination the uterus is likely to be small In Stein s experience there is a 50 per cent chance of palpating the typical ovarian enlargement by bimanual examination although x ray films made after pneumoperitoneum invariably reveal it

The excretion of 17 ketosteroids is normal or slightly elevated in those cases which have been studied (Chapter 20) Gonadotropin assays (FSH) are essentially normal[38,41] and pregnanediol may be excreted in appreciable quantity in some[39,42] but not all[43] instances

At laparotomy both of the ovaries are seen to be greatly enlarged They are somewhat globular in shape and usually 5 to 7 cm in length The capsule is smooth and leathery and is diffusely white save for a light gray motting which is contributed by subcapsular cysts On section the tunica is thickened and dense (Fig 3) Multiple small clear cysts less than 1 cm in diameter are dispersed chiefly near the surface of the gland Microscopically the cysts are seen to be surrounded by a hyperplastic theca interna with some of the component cells containing vacuolated cytoplasm characteristic of luteinization Granulosa cells are usually but not always present in variable number Signs of recent ovulation are rarely if ever in evidence The stroma is relatively dense

The most widely accepted form of therapy is wedge resection of the ovary as introduced by Stein and Leventhal The procedure consists of splitting the ovary longitudinally followed by removal of a generous wedge of tissue in this plane The capsule is reapproximated by simple suture Considering the simplicity of the operation it is remarkable that therapeutic results have been excellent in a great proportion of cases Normal menses are restored in 65 to 90 per cent of the patients and pregnancy occurs in 65 to 70 per cent of those complaining of sterility The hirsutism frequently is little changed but at times is said to disappear dramatically Jones Howard and Langford[44] have

succeeded in restoring ovulatory menses with cortisone in four of six cases. The physiological significance and ultimate therapeutic usefulness of this approach are as yet uncertain.

The pathologic physiology of the Stein-Leventhal syndrome is poorly understood. The fact that masculinization although usually minimal is sometimes of severe grade suggests that androgen may be responsible. The question arises as to whether the ovarian alterations

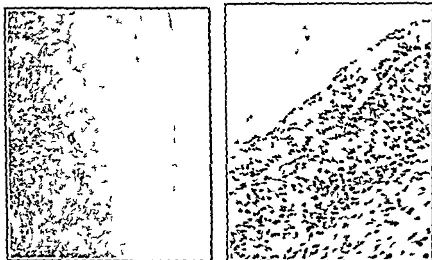


Fig. 8. Sections of the ovary in a case of Stein-Leventhal syndrome. On the left is a low power photomicrograph of the thickened capsule. The higher powered magnification on the right demonstrates *hyperplastic theca lutein cells in the lining of a cyst.*

may be secondary to an excess of such a steroid from the adrenal. Androgen given to experimental animals may produce cystic changes in the ovary (*Chapter 11*). Evidence against such a mechanism in this clinical syndrome includes the usual absence of a substantial rise in 17-ketosteroid excretion as ordinarily seen when masculinization is of adrenal origin. Moreover, although similar changes in the ovary have been encountered in the presence of masculinizing adrenal lesions, such a correlation has not as yet been fully established.

It has been suggested that the hyperplastic and luteinized theca cells may be capable of elaborating either an androgen or a steroid which is metabolized to an androgen.[36, 39, 41, 42, 43] Patients with the syndrome have been reported[45] in which actual nests of lutein-like cells were scattered throughout the stroma in addition to the theca lutein reaction in the cysts. In the guinea pig a spontaneous masculinizing disorder

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cases and spoke of "osteoporotic obesity Baffling was the discovery that patients might exhibit the classical features of some of these syndromes in the absence of apparent adrenal disease The now meaningless term *"pluriglandular syndrome"* was often applied

Looking back at this era one is not surprised that physiological interpretations were totally chaotic Even the existence of specific gonadal adrenal and pituitary hormones was not as yet well established and there was no knowledge whatever of the chemical nature or characteristic physiological activities of such hormones Moreover the fact that tumors of endocrine organs can often (but not always) elaborate excessive quantities of hormone was not fully appreciated The term hypernephroma" was applied to all clear cell or lipoid containing tumors of the kidney gonads or adrenals Present usage of course would distinguish between the clear cell carcinoma of the kidney a nonendocrine tumor as contrasted with tumors consisting of adrenal cortical cells theca lutein cells or Leydig type cells all of which may secrete potent steroidal hormones In spite of this confused state of knowledge Collett[51] in 1924 and Holmes[53] in 1925 successfully removed an adrenal cortical tumor from a girl and woman respectively and witnessed a striking regression of the masculinization A causal relationship was thereby confirmed

In 1932 Cushing[54] described the syndrome which now bears his name His approach differed in two respects from that of most previous authors A series of cases mostly from the literature were categorized primarily on the basis of somatic and metabolic manifestations These included a peculiar adiposity skin changes asthenia osteoporosis and sometimes diabetes Gonadal depression and hirsutism were also present in these patients but masculinization was not severe Cushing pointed out moreover that basophilic tumors of the anterior pituitary were frequently associated with such a syndrome Although not denying that primary adrenal tumors might sometimes be the cause of this same set of symptoms he was of the opinion that the basophilic tumor was the primary lesion in many instances and that it might be responsible for secondary hypersecretion of the adrenal (among other glands) with or without attendant hyperplasia Cushing s delineation of a discrete set of somatic (metabolic) alterations as the basis for a separate syndrome has in the course of time proved to be valid His contention that hyperactivity of the pituitary gland might sometimes be responsible for such a syndrome is also acceptable The present consensus however is at variance with the idea that a basophilic tumor is necessarily of etiologic significance

accompanied by cystic ovaries or atretic corpora lutea has been reported and in the rat chorionic gonadotropin may produce similar alterations in addition to causing constant estrus [48] The histology of the ovarian follicles in the Stein Leventhal syndrome is not greatly dissimilar to that observed during pregnancy or after the administration of chorionic gonadotropin to human subjects [49 50] Although patients with the syndrome do not appear to excrete an excessive quantity of gonadotropin the assay procedure employed measures chiefly FSH and does not rule out an excess of luteinizing hormone

The excellent clinical response to wedge resection of the ovary suggests that the derangement lies primarily within this gland If the hypothesis is accepted that the thickened capsule by its mechanical effect prevents follicle maturation and rupture the thecal hyperplasia might then be accounted for by hormonal derangements resulting from the absence of periodic ovulation

Hyperadrenocorticism

In this category are included disorders considered to be due to hypersecretion of any of a potential variety of adrenal steroids usually but not invariably accompanied by adrenal tumor or hyperplasia and with clinical manifestations consistent with androgen excess—either extreme as in pure virilism or minimal as in Cushing s syndrome

EVOLUTION OF PRESENT CONCEPTS That tumors of the adrenal cortex might be accompanied by masculinization was first noted in the early nineteenth century During the early decades of the present century a number of reports appeared which confirmed this observation and also established the fact that hyperplasia rather than tumor might at times be present Citations to the older literature are given by Collett [51] and by Goldstein Rubin and Aspin [52] Early attempts were made to establish systematic syndromes Because of the prominent hypertrichosis Apert applied the term "hirsutism to all forms of hyperadrenocorticism Because of the secondary sex changes Gallais spoke of the adrenogenital syndrome During this era it was suspected that the adrenal cortex either possessed some function relating to secondary sex structures and body growth or that it exerted a stimulating effect on the gonads According to another popular theory the adrenal was thought to harbor sex cell inclusions which after giving rise to tumors would secrete a masculinizing hormone Compounding the nosologic confusion were cases showing a variety of systemic manifestations Achard and Tiers in describing the diabetes of bearded women attempted to correlate adrenal lesions with hypertrichosis and diabetes Reichman observed osteoporosis in certain

tion of Wilkins[3] it is seen that tumor is the sole cause of adrenal virilism arising before the age of 10 After this age the cause may be either tumor or "acquired hyperplasia Offending tumors may vary in size from 3 to 22 cm They are usually spherical and possess a well defined capsule Of tumors reported approximately 40 per cent show clear evidence of malignancy with metastasis Metastasis is seldom an early feature but when present is likely to involve the liver and lungs The fuchsinophile staining reaction described by Broster and Vines[6] as being characteristic of androgen secreting adrenal le sions although usually present in both tumors and hyperplastic glands is not considered to be pathognomonic Sudds[57] for example has demonstrated the reaction in the normal glands of many subjects over 20 years of age

Manifestations The clinical features of virilism in the female are described at the beginning of the chapter In the presence of either tumor or hyperplasia the 17 ketosteroid excretion is almost invariably elevated well above the normal range With tumors especially the malignant type the output may be extremely high (Chapter 20) The β 17 ketosteroid fraction is usually disproportionately high in cases of tumor as contrasted with hyperplasia but this is not a specific differ ential point An increased excretion of estrogens and of pregnanediol has been found in some cases due to tumor A neoplasm may some times be differentiated from bilateral hyperplasia by its palpability or its displacement of the renal x ray shadow Perirenal air injection sometimes outlines the tumor very nicely (Fig 4) Although this procedure is subject to the hazard of fatal air embolism the newer presacral technique is judged less dangerous in this respect than the high approach A conclusive diagnosis often has been made only by surgical exploration Although extensive studies have not as yet been made it is quite reasonable to presume that cortisone (CXVI) will suppress the 17 ketosteroid output in the presence of acquired hyper plasia as it does in the congenital variety but will not do so in the presence of tumor[102]

Simple precocious puberty in the female although accompanied by growth of pubic and axillary hair is not attended by the high 17 keto steroid excretion encountered in adrenal virilism Moreover the breasts develop as they would at normal puberty menstruation be gins and features of virilism are lacking

Treatment A tumor should of course be removed In instances where the clinical features are colored by admixtures of Cushing s syndrome or if the opposite gland is atrophic it is advisable to ad minister cortisone (CXVI) postoperatively as described under the

Albright[55] in 1941–42 formulated the very important physiological concept which is the basis for our present thinking Cushings syndrome was set apart as a type of hyperadrenocorticism in which the secretion is dominated by S (sugar) hormone(s) known also as glucocorticoids (Selye) Compounds in this category are the 11 oxy or particularly the 11 17 oxysteroids and are of the same family as the currently familiar cortisone (CXVI) and hydrocortisone (CXV) These steroids probably represent the chief secretory products of the normal gland According to Albrights concept the clinical picture of Cushings syndrome could be nicely explained by the capacity of this type of steroid to induce a negative nitrogen balance accompanied by protein depletion and to exert diabetogenic effects The weakness (muscle wasting) osteoporosis (loss of protein matrix) and skin atrophy could all result from a steroid induced protein deficiency

A second type of hyperadrenocorticism was recognized by Albright as being characterized by pure masculinization or virilism due to excessive secretion of N (nitrogen) hormone(s) (testoids) which are pure androgens possessing none of the corticoid properties of cortisone (CXVI) or desoxycorticosterone (CXXI) but as contrasted with cortisone (CXVI) having a protein anabolic effect

Now that cortisone (CXVI) is being widely used clinically it is clearly apparent that both this hormone and ACTH given in sufficient dosage can duplicate the manifestations of Cushings syndrome in complete detail Little doubt now remains that the spontaneous syndrome depends upon excessive elaboration of adrenal steroids of the cortisone family and perhaps in addition compounds with strong effects on sodium metabolism such as aldosterone (CCXX) In pure adrenal virilism the output is dominated by a strong preponderance of androgenic compounds with physiologic activity resembling that of testosterone (VIII)

In the following sections the pure masculinizing syndromes and Cushings syndrome are discussed separately but with full realization that overlap between the two is of common occurrence Probably these hybrid forms depend on a secretion of admixtures of varying proportions of adrenal corticoids and androgens or perhaps they are due in part to individual differences in end organ reactivity The term "adrenogenital syndrome is not employed In the literature this designation has been applied to adrenal disorders of both the hypercorticoid and pure virilizing variety in addition to cases presenting admixtures of the two

ADRENAL VIRILISM IN THE FEMALE—ONSET AFTER BIRTH *Causes* If congenital adrenal hyperplasia is carefully ruled out as in the compila

Thus the urethra and vagina communicate into a small channel which opens externally as a single orifice. The disorder may be conclusively distinguished from postnatal virilism by the demonstration of this defect. The ovaries and uterus remain intact.

The appearance of the external genitalia may be indistinguishable from that of male pseudohermaphroditism in which there is a hypospadic penis and undescended testes. The true sex therefore may be in doubt at birth. Hinman,[8] who tabulated all reported cases of female pseudohermaphroditism, found that 20 per cent at birth were considered to be male and were reared as boys. Probably because of low end organ sensitivity at birth, pubic hair and other secondary structures ordinarily responsive to male sex hormone do not develop immediately in the female pseudohermaphrodite. Pubic hair begins to grow at the age of 1 to 3 years. In gradual sequence thereafter all the typical masculinizing changes of virilism make their appearance. The young male pseudohermaphrodite, in contrast, never shows signs of androgen excess. Sex hair and other puberal changes therefore are not seen until the normal age. An excellent diagnostic point even in early infancy is the high output of 17 ketosteroids in female pseudohermaphroditism.

There is a definite familial incidence of congenital adrenal hyperplasia. Two or more siblings are frequently affected. Transmission to a second generation has not as yet been observed. Such an event would be impossible in an untreated case because of sterility. Adrenal insufficiency occurring shortly after birth may complicate congenital adrenal hyperplasia in the female but is less common than in the male. This problem, along with certain physiological considerations, is discussed in the section dealing with congenital hyperplasia in the male (page 283).

Treatment. Wilkins,[59] Bartter,[60] Jailer[61] and co-workers have shown conclusively that cortisone acetate (CXVI) not only suppresses the excessive excretion of 17 ketosteroids but also leads to regression of the reversible virilizing manifestations. In older subjects breast growth is promoted and ovulatory menses established. Thus the outlook for these patients has improved enormously. Prompt and continued therapy initiated shortly after birth may be expected to suppress the subsequent progressive masculinization. The dose must be adjusted to individual requirements (Fig. 5). The minimal amount which within a week or two restores the 17 ketosteroids to 3 to 8 mg. per day in patients between 8 and 13 years of age and perhaps 1 to 2 mg. per day in very young children is considered optimal by Wilkins.[62] The clinical response also tempers the decision as to a correct dosage

section on Cushing's syndrome In virilism due to hyperplasia sub total resection has not proved to be effective Although little documentation is as yet available one would anticipate benefit from cortisone (CXVI) therapy as described in the following section on congenital hyperplasia

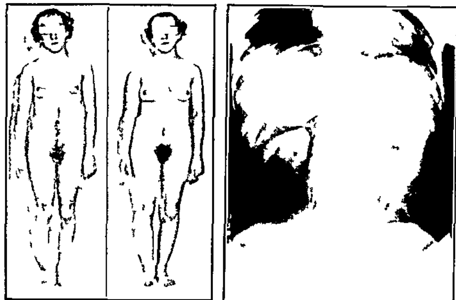


Fig 4 A 23 year old girl with a virilizing adrenal cortical adenoma Note in *the preoperative view on the left the severe hirsutism shrinkage of the breasts* recession of the hair line and rather prominent musculature The picture on the right was taken 6 months after removal of the tumor Distinct improvement is evident although complete reversal subsequently required more than a year Fertility was unimpaired after marriage several years later The x ray photograph made after perirenal air injection visualizes the large tumor on the right

ADRENAL VIRILISM IN THE FEMALE—ONSET IN UTERO (CONGENITAL ADRENAL HYPERPLASIA FEMALE PSEUDOHERMAPHRODITISM MIXED ADRENAL DISEASE OF INFANCY) Wilkins [3] has collected 99 reported cases of congenital adrenal hyperplasia 83 of these were females and 16 were males The disorder is associated with cortical hyperplasia which originates during intrauterine life and persists throughout the lifetime of the patient

Clinical Features In the female at birth the clitoris is noted to be greatly enlarged and the labia majora usually prominent Because of the high output of adrenal androgen during embryonic development the urogenital sinus almost invariably fails to differentiate normally

Previously illustrated in *Human Pathology* by H T Karsner J B Lippincott Co

Penile enlargement and pubic hair growth often are not produced by the latter until several years postnatally even though androgen excess exists at birth Congenital hyperplasia is a very likely diagnosis if siblings are known to be similarly affected or if signs of adrenal insufficiency have at any time been manifest The 17 ketosteroid excretion is of little help since it is elevated in both conditions Extremely high values nevertheless are suggestive of a malignant tumor Perirenal air injection often outlines a tumor for x ray visualization Cortisone (CXVI) is known to depress the 17 ketosteroid excretion in congenital hyperplasia It is reported not to do so if the responsible lesion is a tumor [1, 62] Surgical exploration has often been required in the past to distinguish between these two lesions with certainty It is probable that the response to cortisone may prove to be a specific differential test.

Also to be considered in the differential diagnosis is constitutional or neurogenic sex precocity The status of the testes is a very helpful point In constitutional precocity the testes grow to adult proportions in accompaniment with the other secondary sex changes If an adrenal tumor is responsible the testes usually are of normal infantile dimensions This nevertheless is not an absolute rule Three cases of concomitant testicular enlargement have been reported [63]

PRENATAL ONSET OF ANDROGEN EXCESS IN THE MALE (CONGENITAL ADRENAL HYPERPLASIA, MIXED ADRENAL DISEASE OF INFANCY) *Signs of Androgen Excess* At birth, aside from a rather prominent penis in some cases there may be no detectable sex precocity By the age of 2 or 3 however a distinct enlargement of the penis is followed by growth of pubic hair and the beginning maturation of other secondary sex structures The testes remain small unless invaded by lipoid cells as noted later Because of the suppressing effect of extragonadal androgen it is unlikely that normal testicular development can occur at puberty

Adrenal Insufficiency The term "mixed adrenal disease of infancy" has been applied to certain cases of congenital adrenal hyperplasia in which a serious salt wasting adrenal insufficiency is manifested Males in particular are susceptible to this complication Because of the usual absence of genital precocity in the male in the early interval after birth the diagnosis frequently is not suspected Clinical features of the syndrome were described by Dijkhuizen and Behr [64] in 1940 In the same year Wilkins Fleischmann and Howard [65] and Butler Ross and Talbot [66] first recognized the component of adrenal insufficiency Knudson [67] has presented a series of cases and cited additional literature.

Overtreatment will produce symptoms of Cushing's syndrome The usual intramuscular dose is 5 to 25 mg a day or 20 to 100 mg every 4 days The oral dose varies from 10 to 75 mg daily divided in two or three doses

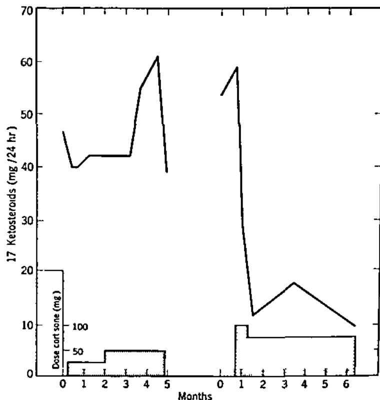


Fig 5 17 Ketosteroid excretion in a 14 year old girl with congenital adrenal hyperplasia Note the critical dose level of cortisone which was required to suppress the 17 ketosteroids Neither 25 mg nor 50 mg daily by mouth were effective whereas 75 mg reduced the output to normal Menses appeared within 2 months and facial hair growth previously controlled in part by electrolysis ceased to progress Two years after therapy was begun a dose of 50 mg proved to be satisfactory for maintenance

POSTNATAL ONSET OF ANDROGEN EXCESS IN BOYS (PRECOCIOUS PSEUDO PUBERTY An adrenal disorder giving rise to androgen excess in young boys if not the result of *congenital* adrenal hyperplasia is perhaps without exception always due to tumor There is at least an even chance that the tumor will be malignant Males are much less frequently afflicted than females In the very young child a clinical distinction between tumor and congenital hyperplasia may be difficult

sates by secreting an increased amount of ACTH (Elevated blood levels of ACTH have been demonstrated[71]) Adrenal hyperplasia and hypersecretion ensue but because of the aforementioned intrinsic defect the predominant secretory products are androgenic The faltering secretion of hydrocortisone (CXV) may then be largely restored by the excessive level of ACTH In some patients however

TABLE 4

ADRENAL FUNCTION IN CONGENITAL ADRENAL HYPERPLASIA *

Specific H[illegible]	Congenital Hyperplasia				
	Hypothetical State of Initial Secretory Defect Not Compensated	After Initial Secretory Compensation			
		N[illegible] Adrenal Insufficiency	Adrenal Insufficiency	No Adrenal Insufficiency but Hypertension	During Cortisone Therapy
ACTH	Normal	High	High	High	Normal (inhibited by [illegible])
Cortisone family	Low (intrinsic adrenal defect)	Normal†	Normal†	Normal†	Normal ([illegible])
Aldosterone and DOCA family	Probably normal	Normal	Low (intrinsic defect)	High (forced by ACTH)	Not high
Androgen family	Not less than normal	Very high	Very high	Very high	Normal (because ACTH down to normal)
Estrogen family	Not less than normal	Increased	Increased	Increased	Normal

* A [illegible] based on [illegible]

† Forced up by high ACTH output

the potent salt retaining adrenal steroids still cannot be manufactured normally Salt wasting adrenal insufficiency thus complicates the picture Of interest is the fact that the zona glomerulosa of the adrenal may be absent in histological sections In certain cases of this disorder the electrolyte function of the cortex is not lost but perhaps may be actually stimulated and lead to the hypertension which is sometimes encountered Gonadal failure in the mature individual is easily explained by the depressing effect of excessive amounts of androgen (plus some adrenal estrogen) on the output of pituitary gonadotropin Cortisone (CXVI) therapy by artificially providing a normal amount of pituitary inhibitor relieves the pituitary of secreting excessive amounts of ACTH With the reduced production and

Signs of the adrenal insufficiency usually consist of persistent and projectile vomiting beginning a few days or weeks after birth This symptom along with visible peristalsis falsely suggests gastrointestinal obstruction Dehydration becomes apparent and chemical studies are likely to reveal a depressed blood bicarbonate sodium and chloride an azotemia and an elevated potassium Diagnosis is confirmed by the demonstration of high urinary 17 ketosteroids along with a favorable therapeutic response to saline infusions and desoxycorticosterone (CXXI) The latter in doses of 1 to 5 mg a day preferably combined with 2 to 5 grams of extra salt is effective in controlling the salt depletion which characterizes the syndrome The most rational form of long term therapy would include cortisone (CXVI) This hormone in addition to inhibiting the androgen excess which eventually will be manifest also possesses appreciable sodium retaining activity In addition to cortisone (CXVI) extra salt may be the only supplementary therapy required Some patients however need desoxycorticosterone (CXXI) in addition [68]

Hypertension An occasional patient with congenital hyperplasia whether a boy or a girl exhibits hypertension rather than adrenal insufficiency The blood pressure is effectively lowered by cortisone (CXVI) in optimal dosage [69]

In a certain number of boys with this syndrome an extensive infiltration of the testes with large lipoid containing cells has been demonstrated Most observers have identified these cells as aberrant adrenal cortical tissue However Landing and Gold [3] consider them to be Leydig cells grown hyperplastic in response to an excess of tropic hormone (LH?) thrown out along with ACTH by the anterior pituitary

Physiology of the Disorder The studies of Bartter [60] Wilkins [59] Jailer [61] Lewis [0] and co workers have aided greatly in the elucidation of the pathophysiology When ACTH is given to these patients the 17 ketosteroids rise (as they do normally) Neutral reducing steroids (11 oxysteroids) however do not rise adequately *Moreover the fall* in eosinophils is impaired and the normal response of sodium retention does not occur Salt actually tends to be excreted in increased amounts The administration of cortisone (CXVI) to these patients reduces the excessive excretion of 17 ketosteroids and biologically active androgens Estrogens and pregnanetriol (LXIII) [103] which frequently are elevated also decline

The following hypothesis seems justified Owing to an intrinsic defect of the adrenal cortex the cortisone (CXVI) family of steroids is not secreted in adequate amount (Table 4) The pituitary compen

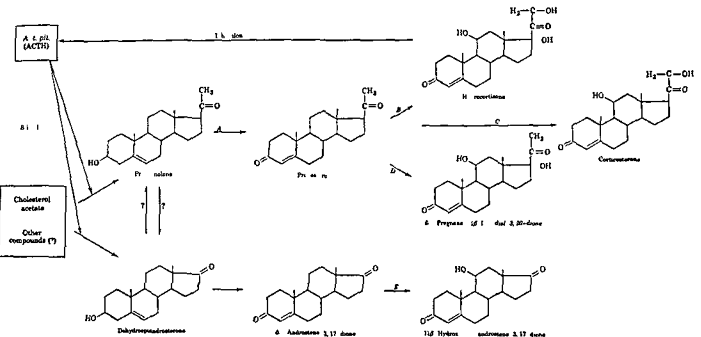


Fig 6 Hypothetical scheme of adrenal steroidogenesis The nature of the initial transformations in the two pathways is not as yet clear Interconversion within the adrenal between the upper 21 carbon and lower 19 carbon series is probably of minor importance if it occurs at all Degradation of a small component of 21 carbon compounds to 17 ketosteroids does occur in systemic or hepatic tissues Preformed androgens likewise are *susceptible to further alteration*

release of ACTH the adrenals no longer are made to secrete excessive quantities of androgen Not very well explained is the tendency of patients with this disorder actually to lose salt under the influence of administered ACTH Elaboration of a separate salt losing adrenal hormone has been postulated[68 70] Such a theory would also explain the rather large requirement of desoxycorticosterone (CXXI) for maintenance as compared to the Addisonian patient

Speculation may be made as to the existence of specific defects of steroidogenesis which might produce such a syndrome The scheme postulated in Fig 6 represents a series of steroids in process of chemical transformation within the gland It may be seen that ACTH is shown to initiate a chain of events in two independent pathways Thereafter in each pathway the conversions are accomplished by enzymes which do not require the mediation of ACTH The first enzyme promotes dehydrogenation in both series at position 3 of the molecule In subsequent stages other enzymes three in number serve to introduce a hydroxyl radical at positions 11 17 or 21

The major pathway at the top of Fig 6 is composed of compounds with twenty one carbon atoms The terminal carbon at the end of the two carbon chain represents position 21 It may be seen that hydrocortisone (CXV) and corticosterone (CXIX) are important end products of this series The pathway at the bottom of the figure is represented by steroids which contain nineteen carbon atoms and possess androgenic activity

The aberration in congenital adrenal hyperplasia could be explained by assuming an impairment in hydroxylation at position 21 Synthesis of hydrocortisone (CXV) thus being deficient an inadequate inhibition of the secretion of ACTH would ensue Excessive elaboration of ACTH would now overstimulate the intact lower pathway and lead to masculinization Although the anticipated enhancement of pregnenolone (XI) formation might promote the manufacture of daughter corticoids by providing an increased pool of precursor thus compensating for the enzymatic defect the kinetic advantage would still remain with the androgen series There is no evidence that a defect in hydroxylation at position 11 exists in either major pathway Indeed urinary steroids in this disorder include increased quantities of metabolites with a hydroxyl group in this position (Chapter 20 Table 35)

Treatment Control of complications due to electrolyte deficit has been mentioned previously Other features of the condition which assume importance as maturity approaches are stunting of body stature resulting from accelerated epiphyseal closure and sterility due to suppression of FSH by adrenal androgen Continual administration of

be remembered that overlap occurs with states of pure virilism Cases of typical Cushing s syndrome are illustrated in Fig 7

Obesity An increase of subcutaneous fat in adults is characteristically confined to the face neck and trunk In infants and children the extremities may share in the adiposity The face is conspicuously rounded and the cheeks are very prominent

Skin The face is dusky red or occasionally bright red in color Acne may occur Wide purple striae atrophicae often develop over the lower abdomen and hips The skin in general is somewhat thin perhaps with a pink tint and bruises easily

Hair In the female hirsutism of mild or moderate degree involving the face and trunk is common Conspicuous baldness is uncommon

Muscles Generalized muscular weakness is a very significant complaint A diagnosis would be made with considerable reluctance in the absence of this symptom In advanced states of the disorder the patient may be too weak to leave the bed Atrophy of the leg and arm muscles may be clearly apparent Flabbiness of the abdominal wall leads to pendulous protrusion A low creatinine excretion attends the muscle atrophy

Bones Osteoporosis of the spine is very common and is a very important diagnostic finding Compression of the vertebral bodies by the interposed discs produces the "fish spine" as visualized by x ray Compression fractures are a likely complication and the resulting kyphosis frequently is evident on physical examination

As contrasted with the pure masculinizing syndromes epiphyseal development in the child tends to be delayed

Cardiovascular Hypertension atherosclerosis and nephrosclerosis are not only very frequent but complications arising therefrom are often responsible for a fatal outcome

Sex Organs In the female amenorrhea and in the male impotence are typical The presence of clitoral hypertrophy is variable

Blood Cells Polycythemia is common Neutrophils tend to be high and lymphocytes low[74] The fasting eosinophil count is low Although representative statistics are as yet meager an absolute eosinophil count below 50 per cubic millimeter is to be anticipated

Metabolic Changes Protein wasting is undoubtedly of constant occurrence yet a negative nitrogen balance cannot always be demonstrated Perhaps the average daily decrement is too small to detect or else depletion may have already reached its limit by the time such a study is made

cortisone (CXVI) during early childhood should serve to prevent the premature closure of growth centers. Cases are reported in which this hormone has promoted normal testicular growth and spermatogenesis in older boys.[98]

CUSHING'S SYNDROME: CLINICAL FEATURES. Of 166 cases of Cushing's syndrome collected from the recent literature 136 were females and

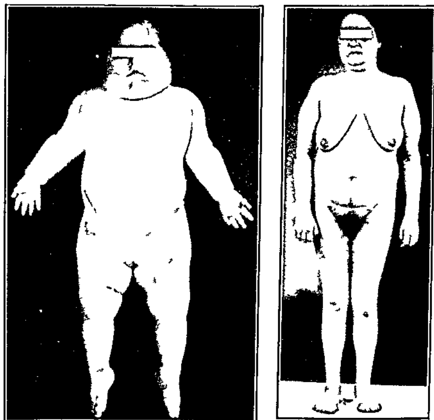


Fig. 7. Cushing's syndrome on the left in a 3-year-old girl and on the right in a 39-year-old woman. Exploration of the adrenals did not reveal tumor in either instance. The young girl ultimately grew more hirsute and the voice became deep. Pituitary irradiation was followed by a temporary decrease in adiposity and increased strength. The woman showed little response to similar irradiation and ultimately succumbed to a fulminating meningitis.

30 were males. Ages have ranged from early childhood to the seventh decade. Diagnosis of Cushing's syndrome depends on the judgment of the clinician as to whether the clinical and laboratory data are sufficiently typical. No single laboratory finding is in itself diagnostic. The syndrome in its "pure" form is described. It should nevertheless

of muscle bone and skin the obesity diabetes hypertension blood cell alterations and electrolyte changes are all compatible with corticosteroid excess Other manifestations such as mild hypertrichosis acne and gonadal depression seen in relatively pure forms of Cushings syndrome although consistent with an androgen excess might be attributable to androgenic material derived from the metabolic degradation of corticosteroids (Chapter 7) Pure cortisone (CXVI) or hydrocortisone (CXV) administered to normal subjects may produce these same manifestations

In cases of Cushings syndrome due to benign adrenal tumor the urinary 17 ketosteroids do not tend to rise (Chapter 20) This suggests that preformed androgen is not produced in excess but that the tumor cells are capable of selective elaboration of corticoids (upper pathway of Fig 6) These compounds are degraded only in small part to active androgens or 17 ketosteroids In cases associated with adrenal hyperplasia where an excessive secretion of ACTH may be postulated as the primary cause of the disorder one would predict that an increased synthesis of androgen should accompany the accelerated formation of corticoids (Fig 6) 17 ketosteroid excretion does in fact tend to be somewhat elevated in such patients The physiological effect of these androgens is nevertheless overshadowed by the pronounced influence of the abundant corticoids Malignant adrenal tumors are frequently attended by a massive excretion of both corticoids and 17 ketosteroids Both synthetic pathways are undoubtedly operating at accelerated rates Varying admixtures of severe virilizing phenomena could occur if androgen synthesis were particularly prominent Since the tumor consists of autonomously functioning tissue not controlled by ACTH serious alterations in the ratio of corticoids to androgens would not be surprising An exclusive increase of androgen synthesis would of course produce pure virilism rather than Cushings syndrome That tumors may function in such manner has been pointed out in a previous section

That excess estrogen may be secreted in Cushings syndrome is evidenced by its increased titer in the urine in some cases along with attendant physiological changes such as breast development and uterine bleeding sometimes seen in immature girls It is unlikely that the estrogen is derived from secondary degradation of corticoids

Whereas adrenal tumor is almost without exception the cause of Cushings syndrome in the immature child it is of less frequent occurrence in the adult Both in the compilation of Thompson and Eisenhardt[80] and in the single series of 64 cases reported by Sprague Kvale and Priestley[78] only 22 per cent resulted from adrenal neo-

Frank diabetes is not invariable, but an impaired glucose tolerance is the rule Polyuria and polydipsia are sometimes experienced even in the absence of glycosuria This phenomenon may be related directly to the water excreting function of the kidney

Inconstant findings consist of a slight increase in BMR elevated serum cholesterol high serum CO_2 slightly elevated sodium and depressed chloride and potassium

When both salt and desoxycorticosterone are administered to patients with Cushing s syndrome there is usually a salt diuresis rather than the normally expected retention [92]

Eyes Exophthalmos has been described but not verified by quantitative measurements

Nervous System Severe depression is reported in 25 per cent of the cases Psychoses are common and suicide is by no means rare [75]

Infection Increased susceptibility to overwhelming infection is a serious hazard of Cushing s syndrome and is very prominent among the causes of death

Hormone Assays Urinary corticosteroids tend to be high when estimated by bioassay [6] and also when determined chemically as neutral reducing compounds [77] or formaldehydogenic substances [78] and yet although these excreted steroids are of the very category thought to be responsible for the disease approximately 10 per cent of the cases overlap the normal range This is less common in the presence of tumor than with hyperplasia That an overlap with normal is ever obtained may be due partly to inconstancies in the metabolic degradation of parent steroids during their sojourn in the body before excretion and partly to variations in the proportion of conjugated to unconjugated (extractible) urinary steroids

The excretion of 17 ketosteroids is highly variable in Cushing s syndrome In general the values tend to be slightly elevated in the presence of adrenal hyperplasia markedly elevated in some but not all cases of malignant tumor and not altered in the presence of a benign tumor (Chapter 20) Considerable overlap occurs not only between these groups but also with the normal range In a limited series of cases a fall in 17 ketosteroid excretion has usually been observed after cortisone administration when the disorder was caused by hyperplasia but not in the presence of an adrenal tumor [79, 10]

Causes of the Physiologic Derangement As stated in the introduction to this section there is little doubt that an excessive secretion of corticosteroids is the immediate primary cause of Cushing s syndrome A source in the adrenal is obvious in cases due to a tumor of this gland Of the various manifestations of the disease the atrophy

of muscle bone and skin the obesity diabetes hypertension blood cell alterations and electrolyte changes are all compatible with corticosteroid excess Other manifestations such as mild hypertrichosis acne and gonadal depression seen in relatively pure forms of Cushing's syndrome although consistent with an androgen excess might be attributable to androgenic material derived from the metabolic degradation of corticosteroids (Chapter 7) Pure cortisone (CXVI) or hydrocortisone (CXV) administered to normal subjects may produce these same manifestations

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plasm The remaining majority showed either hyperplasia or no gross lesion Of a total of 52 cases of tumor reported in the recent literature 27 were called malignant All tumors so far reported in males have been malignant

Of cases of Cushing s syndrome not due to adrenal tumor most exhibit adrenal hyperplasia but a minority show no clear-cut anatomical abnormality With the possible exception of masculinizing ovarian tumors which may produce mild manifestations of Cushing s syndrome it is likely even in the absence of hyperplasia that cortical hypersecretion exists in all instances Although thymic tumors have been found in several cases adrenal hyperplasia also was present[81] It is reasonable to suppose that the commonly observed cortical hyperplasia is caused by hypersecretion of ACTH The clinical improvement which may attend x ray irradiation of the pituitary or partial destruction of the gland[105] is in keeping with such an hypothesis Somewhat against this notion is the failure of various investigators[106] to demonstrate high levels of ACTH in the blood of affected patients Such negative results however are not conclusive because assay methods are not sufficiently sensitive to measure the level of ACTH in the plasma of normal subjects

It is pertinent to consider the significance of basophilic adenoma which was stressed by Cushing as being of etiological significance These tumors have rarely exceeded a few millimeters in diameter It has been well established that similar tumors or aggregations of basophilic cells are found in 2 to 7 per cent of patients at routine autopsy and produce no clinical manifestations during life[82] This of course does not prove that such tumors cannot at times be functional Eosinophilic tumors of the pituitary for example are in some instances nonfunctional but in other individuals will produce acromegaly Non functioning tumors of the adrenal cortex likewise are not rare[83, 84, 10] The fact that 33 of 52 patients with Cushing s syndrome as compiled by Thompson and Eisenhardt[80] showed basophilic tumors indicates a much higher incidence than in the normal population To identify the tumor as a source of ACTH on the other hand and thus as the primary cause is not allowable on the basis of correlation alone Although the cell of the pituitary which secretes ACTH is not known[8] the eosinophile is perhaps more favored than is the basophile Moreover both eosinophilic and chromophobic tumors have been described in patients with Cushing s syndrome[54, 80] That the hyalinization of the basophiles described by Crooke[86] and seen in over 90 per cent of cases of Cushing s syndrome as compared to 3 per cent in routine

autopsies is undoubtedly a secondary phenomenon is attested by its development when the causative lesion is an adrenal tumor and also when cortisone (CXVI) is administered[87] It therefore is possible that all *anatomic changes so far described in the pituitary are not related* to the supposed primary physiological defect of this gland which is thought to be responsible for many cases of the syndrome Heinbecker[8] demonstrated atrophy of hypothalamic nuclei in five cases of Cushing's syndrome not caused by an adrenal tumor This finding suggests that a primary hypothalamic disorder may in some cases be responsible for hypersecretion of ACTH

Prognosis and Treatment Cushing estimated the average duration of life in patients to be 3 to 7 years with death most commonly due *to sepsis or hypertensive disease Occasional cases not due to adrenal* tumor may undergo spontaneous temporary remission or may manifest a cyclic fluctuation in severity

It is imperative that an adrenal tumor be ruled out before any treatment other than adrenal surgery is even considered X ray procedures, including perirenal air injection sometimes suffice but bilateral exploration is frequently required When a tumor is found the opposite adrenal is seen to be atrophic as a result of a suppression of ACTH output by the autonomously functioning tumor Because of this atrophy fatal adrenal insufficiency will most certainly follow removal of the involved gland unless cortical hormone is administered *It is advisable to give several hundred milligrams of cortisone* (CXVI) daily immediately before and for several days after surgery then to taper the dosage and perhaps to administer ACTH in addition so as to reverse the atrophy more promptly

If an adrenal tumor has been ruled out satisfactorily conservative therapy would consist of X irradiation to the pituitary with the hope of reducing its ACTH output Many patients enjoy at least a temporary remission after radiation Cushing employed this procedure and it is still being recommended[89] As the most definitive therapeutic approach it is likely that subtotal or possibly total adrenalectomy will enjoy increasing favor for severe forms of the disease Both the latter *approach which was once out of the question* and the former once exceedingly hazardous may be performed with reasonable safety now that cortisone (CXVI) is available for postoperative support and if necessary for indefinite maintenance The Mayo Clinic group convinced as early as 1932 that even in the absence of tumor the adrenal plays a dominant role pioneered in this procedure Their most recent series of cases of radical extirpation reveals a high percentage of

favorable remissions and a low operative mortality [8] Poutasse and McCullagh likewise have had good results with subtotal adrenalectomy [89]

Sex precocity of intracranial origin

It may be predicted that a rise in the output of pituitary gonadotropin occurring ahead of its normal puberal schedule will result in precocious sex development Although primary pituitary lesions such as tumors are not among the recognized causes of such precocity tumors of the hypothalamus and pineal region are known to produce it A type of spontaneous sex precocity unassociated with a lesion anywhere in the body is also well known This type of precocity is generally believed to depend on an accelerated maturation of hypothalamic centers which control the release of hypophyseal gonadotropin Both types of premature puberty have been encountered in children as young as 2 years of age These two varieties of precocity are characterized by a complete isosexual puberal development in which the gonads themselves attain a mature functional status and elaborate their characteristic hormones The subject of intracranial sex precocity has been carefully reviewed by Seckel [2] Weinberger and Grant [90] and Bing Globus and Simon [91]

LESIONS OF THE PINEAL AND HYPOTHALAMUS Pineal neoplasms long known to be associated with sex precocity actually produce such a disorder in only about one third of the cases After much experimental work no acceptable evidence has been presented that either a pineal tumor or the normal gland itself elaborates any hormonal product concerned with sex maturation There is on the other hand increasing evidence that the hypothalamus in some unknown fashion is concerned with the secretory activity of the anterior pituitary It is significant that when pineal tumors are accompanied by sex precocity the adjacent hypothalamus invariably is encroached upon by the neoplasm Moreover it has repeatedly been observed that various hypothalamic tumors and other primary lesions which do not implicate the pineal gland can produce the same syndrome

It has been postulated [90] that the hypothalamus harbors certain nuclei or nerve tracts which during prepuberal life inhibit the secretion of gonadotropin by the anterior pituitary If these areas are destroyed by disease a disinhibition of the pituitary allows gonadotropin to be released prematurely An alternate theory would interpret pituitary hyperactivity as resulting from irritation (stimulation) of nerve structures which normally stimulate the hypophysis during and after puberal development

Clinical Manifestations In a young girl there is no evidence of androgen excess as characterized by virilization This is emphasized by the fact that pubic and axillary hair tend to lag behind the growth of breasts and female genital organs The clitoris is not enlarged. It would seem that the pituitary releases only gonadotropin which in its usual manner stimulates the ovary to attain functional and anatomic maturity and to secrete the normal ovarian hormones

Sex precocity due to a lesion of the hypothalamic area is five times as common in boys as in girls Pineal tumors are twenty times as common In males the testes responding in normal fashion to the pituitary stimulus rapidly grow to adult proportions Spermatogenic function is attained and the simultaneous stimulation of Leydig cells leads to an adrogen output which would be normal for the adult but not for the immature child The excretion of 17 ketosteroids tends to be high for the chronological age but does not exceed normal adult levels Urinary gonadotropin theoretically should be detectible however extensive data on this point are not available The most important differential point which distinguishes this type of macrogenitosomia from the adrenal variety is the presence of mature testes

To prove that a case of precocious puberty is due to a lesion of the hypothalamic area and is not an instance of simple physiologic precocity it is required that neurological stigmata or other localizing signs be demonstrated A history of encephalitis is suggestive of previous brain damage from the inflammatory reaction A tumor will almost always reveal itself as a neurological problem within 1 to 2 years The posterior hypothalamus is more closely related to sex precocity than the anterior area Because of the proximity of the third nerve nucleus palsies of the ocular muscles and changes in the pupil are commonly associated with a tumor located in or near the pineal area It is not rare to encounter a variety of other complications arising from the involvement of near by hypothalamic centers [90] Included are diabetes insipidus obesity hyperthermia and sleep disturbances Increased intracranial pressure and hydrocephalus due to local blockage are common

A tumor in the hypothalamic region carries a poor prognosis Successful removal is difficult, if not impossible

IDIOPATHIC SEX PRECOCITY (SIMPLE EARLY PUBERTY) This is an extreme physiologic variant in which the clinical manifestations of sex precocity are indistinguishable from those accompanying hypothalamic lesions Missing from the picture are (1) a history of disease or injury which might have damaged the brain (2) neurologic disturbances and (3) other stigmata of hypothalamic involvement Gonado

tropin excretion is in the adult range[96] Life expectancy is normal The cause is probably a premature maturation of hypothalamic centers concerned with the release of pituitary gonadotropin A case of simple idiopathic precocity is illustrated in Fig 8

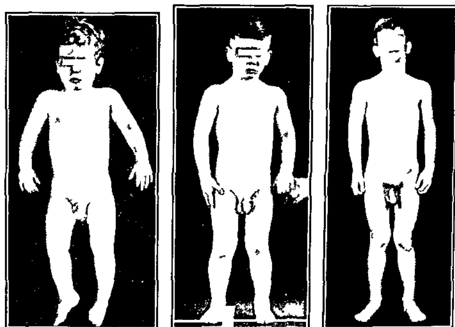


Fig 8 A boy with simple sex precocity who shows premature puberal development of the complete type The first photograph was taken at the age of 15 months the second at 2 years and the third at 4 years Note that precocious testicular development is an early manifestation and that it is followed by penile enlargement and then by growth of pubic hair Gonadotropin excretion was 4 mouse uterine units at 2 years of age and 64 units at 4 years of age 17 Keto steroids were 2 8 mg at age 4

Premature Growth of Sex Hair

Silverman and co workers[93] have studied 29 children (28 girls 1 boy) who developed pubic hair and sometimes axillary hair before the age of 8 and whose development was followed long enough to rule out organic disease In the girls neither breast development nor menses were observed until later on at the usual age and estrogen excretion was not prematurely increased There was no other increase of body hair and no clitoral enlargement or other indication of severe andro gen excess The boy showed no genital enlargement until the onset of normal puberal development at the expected age

This condition appears to be a physiologic variant which might be ascribed either to an unusual intrinsic precocity of the hair follicles or to a premature "adrenarche" which antedates pubarche By adrenarche is meant the augmentation of adrenal androgen secretion believed to accompany normal puberal development. The potency of adrenal androgens is of a low order If such steroids were secreted prematurely in physiologic amounts complete masculinization would not be anticipated Suggestive of premature adrenarche as the cause of this condition is the finding that statural development epiphyseal maturation and 17 ketosteroid excretion tend to exceed the average for the given chronological age

Perloff and Nodine[84] have described 4 children with congenital quadriplegia who showed precocious pubic and axillary hair slight penile or clitoral enlargement and 17 ketosteroids slightly above average for the age Gonadal maturation was not present The authors suggest that a premature adrenarche may have been caused by the brain lesion which in addition to being in the cortex was also present in some specialized hypothalamic center normally concerned with the hypophyseal control of adrenal androgen secretion

Idiopathic Hypertrichosis

Excessive hair growth in the adult woman unrelated to organic disease of the adrenal cortex or ovary is the most common variety of hirsutism encountered clinically The growth of hair on the face may be fully as abundant as when masculinizing lesions of the ovary or adrenal are present Hair on the chest linea alba and extremities may resemble that of the male Lengthening of the hair is usually first noted shortly after puberty There may be a history of familial incidence A transient type of hirsutism is occasionally observed during pregnancy

In its pure form unaccompanied by clitoral hypertrophy a deep voice infertility amenorrhea or by any of the elements of Cushing's syndrome the cause might well be related to an unusual sensitivity of the pilary system to normal levels of circulating androgen On the other hand the fact that 17 ketosteroid excretion in many patients tends to exceed the average for adult women suggests that androgen secretion from the adrenal or perhaps the ovary is in some cases relatively high It is pertinent to remember that 17 ketosteroid excretion in the normal female averages about 4 to 5 mg per day below that of the male This seems small yet in order to raise the excretion in the average female to that of the average male approximately 10

mg of testosterone propionate (LXXXIX) daily is required This is a frankly virilizing dose Because many women normally excrete more 17 ketosteroid material than the average man it is not illogical to suspect that secreted androgens or potent androgenic metabolites in certain women may sometimes be sufficiently abundant to promote the growth of male sex hair and even to lead to more severe virilization

If in addition to hirsutism a patient by chance is obese has menstrual irregularities and is infertile a confusion with the Stein Leventhal syndrome is not easily resolved without ruling out polycystic ovaries Should hypertension or diabetes also be present it may be difficult to rule out an early or mild Cushing s syndrome The latter diagnosis however cannot be made without more specific evidence of corticoid excess A further discussion of simple hirsutism with citations to the literature may be found in Chapter 20

The only treatment for simple hirsutism known at present consists of removal by shaving or epilation Cortisone (CXVI) in small doses will often reduce the 17 ketosteroid excretion [44, 101] but although there is suggestive evidence that hair growth may diminish the hormone has not been given sufficient trial for adequate evaluation in this regard Such a response would not be anticipated in less than 6 to 12 months

Differential Diagnosis

In the following tables brief outlines are presented of some diagnostic points which are useful in differentiating the various categories of androgen excess from each other and from other confusing disorders

TABLE 5

Differential Diagnosis of Androgen Excess in Prepuberal Boys

	Leydig Cell Tumor of Testis	Congenital Adrenal Hyperplasia	Adrenal Tumor	Simple Precocious Puberty	Precocity of Hypothalamic Disease	Premature Growth of Sex Hair (Idiopathic)
Usual age of onset	4–8 years	[illegible] Ketosteroid high at birth. [illegible] and pubic hair age [illegible]	Not characteristic	After age [illegible]	After age [illegible]	Not characteristic
Siblings often affected	No	Yes	No	Occasionally	No	?
Size of testes	Unilateral enlargement	Small	Small	Bilateral enlargement	Bilateral enlargement	Normal for chronological age
Spermatogenesis	No	No	No	Yes	Yes	No
Ultimate effect on secondary sex characters	Complete maturation	Complete maturation	Complete maturation	Complete maturation	Complete unless death intervenes	Pubic and axillary hair only
17-Ketosteroid excretion	Elevated—may exceed adult normal	Elevated—may exceed adult normal	Elevated—may exceed adult normal	Usually high for age—not above adult normal	Usually high for age—not above adult normal	Normal but sometimes higher than avg. for age
Effect of cortisone (CXVI) on 17-KS excretion	Presumably none	Sharp decrease	None	Presumably a decrease †	Presumably a decrease †	Presumably decrease †
Salt-losing adrenal insufficiency	No	Common	No	No	No	No
Therapy	Excision	Cortisone (CXVI) (salt and DOCA if indicated)	Excision	None indicated	Surgery rarely successful	None indicated
Prognosis as to life expectancy with proper treatment	Good	Good	Depends on malignancy of tumor	Good	Poor if due to tumor	Good

The testis may be quite large if [illegible] cell infiltration complicates the [illegible]
† Small doses of cortisone (CXVI) reduce 17-ketosteroid excretion in normal subjects (adrenal suppression).

TABLE 6

Differential Diagnosis of Androgen Excess in Prepuberal Girls

	C g tal Adrenal Hyperplas	Virilizing Adr al T mo	Simple Precoc us Puberty	Precoc ty f m Hypothala ic Disease	Prematur Gro th f Sex Hair (Idiopath)	Cushing s Syndrome
Usual g f set	17 ketoster d h gh at b th Cl to is large t birth P o-gressive v l-i atio f m age 1 t 3	Not har c-teristi	Afte age 1 to 2	Afte age 1 to 2	N t charac-te istic (any t m fter 6 th)	N t haracter ist c
S blings ofte ff cted	Y	N	Occasio lly	No	?	No
P co us b east development and me stru ation	N	Rarely (Ref 96 9)	Yes	Yes	No	O e-fourth f as s (R f 63)
Obes ty	No	No	N	M y cc r	No	Y s
Ult mate d g ee f l ation (m le x hair cl to is)	S	Se e	N	N e	None	Var able
U ogenital si s	P ese t	Absent	Abse t	Abs t	Abse t	Abse t
Hype ten ion	S met mes	N	N	No	N	Yes
Statural dev lop-m t a d bo ge	Ad anced	Ad ced	Ad ed	Adva d	Sl ghtly ad a ed	Ofte r tarded
Salt-los g d re al nsuffi c ency	Oc ur b t less comm th males	N	No	N	No	No
17 k toste d t	El ted—m y eed dult rmal	Ele ted—may eed ad lt ormal	Normal t slightly h gh f age b t t bove adult o m l	Presum bly sam as p e-ced g l-umn	Normal b t slightly abo e a er ge f r age	Adr al hype plasia ormal to slightly le-ted Adr al ade-noma ormal Adr nal cancer may be very high but can be ormal.
Effect of t so (CXVI) l KS ex tion	Sharp dec ease	N	Pres m bly a de-a t	P es mably dec ease †	Presumably de-crease †	Fall w th hype plasia ? No ha g th tumor ?
Th rapy	C tiso e (CXVI) (salt and DOCA f d ted)	E is	N	Surg y r ly cessf l	No e	E se t mor l hyperplasia adiate pitui tary or ad e-lectomy
Prog os s as t l fe pe ta y w th p per t atm t	Good	Depe ds o mal g an y f t m	Good	I oo f due to tu or	Good	Good I adr l ade ma is c ssfully re-m d P b-bly good th adre al tomy f hype plasia

An admixture f features f Cushing s yndrome a d virilism is t e listings in these col ns ar based the pur f m f e ch
† Small doses f co tiso (CXVI) ed ce 17 k toste d e ti mal s bjects (ad l t p ess)

TABLE 7

DIFFERENTIAL DIAGNOSIS OF ANDROGEN EXCESS IN POSTPUBERAL WOMEN

	Adrenal Virilism		Masculinizing Ovarian Tumor	Stein-Leventhal Syndrome	Cushing's Syndrome*	Simple Hirsutism (Idiopathic)
	Tumor	Acquired Hyperplasia				
Usual age of onset	Not characteristic	Probably in younger age group	Not characteristic	16 to 30	Not characteristic	Near puberty
Obesity	No	No	Rare†	3[illegible] of cases	[illegible]	No
Hypertension	No	No	Sometimes†	Uncommon	Yes	No
Purple striae	No	No	No	No	Common	No
Impaired glucose tolerance	No	No	Sometimes†	No	Common	No
Polycythemia	Sometimes slight	Sometimes slight	Sometimes†	No	Common	No
Low [illegible]	Normal	Normal	Probably normal	Probably normal	Low	Normal
Muscle atrophy and weakness	No	No	No	No	Very important finding	No
Osteoporosis	No	No	No	No	Very important finding	No
Hirsutism	Severe	Severe	Severe	90% of cases moderate to severe	Very common but of moderate degree	Mild to severe
Baldness	Common	Common	Common	No	Uncommon	No
Clitoral hypertrophy	Yes	Yes	Yes	Not common	Absent or mild	Rare
Breast atrophy	Yes	Yes	Yes	No	Not significant	No
Amenorrhea	Yes	Yes	Yes	Yes	Yes	No
17-Ketosteroids	Abnormally high	Abnormally large	Usually normal, sometimes elevated	Usually normal or slightly elevated	See Table 6	Normal, somewhat above average
Corticosteroid excretion	Normal	Normal	Normal†	Normal†	High in 90%	Probably normal
Effect of cortisone (CXVI) on 17-KS	No	Immediate reduction	Probably lowered‡	Lowered‡	See Table 6	Lowered‡

* An admixture of features of Cushing's syndrome and virilism is not rare. Listings in these columns are based on pure forms of each.

† Mild manifestations of Cushing's syndrome are not uncommon in masculinizing ovarian tumors.

‡ Small doses of cortisone reduce 17-ketosteroid excretion in normal subjects (adrenal suppression).

TABLE 6

DIFFERENTIAL DIAGNOSIS OF ANDROGEN EXCESS IN PREPUBERAL GIRLS

	C g t l Ad er al Hyp rpla i	Viril i g Adre al Tumor	S mple Pr o i us Pube ty	Pr o ty f m Hypothal m c Disease	Prem ture Growth of Sex H ir (Id op th c)	Cush g s Sy dr me
Usual age of on set	17 ketostero d h gh t birth Clito large at b rth Pro g ess ve vir l iz t f m age 1 to 3	N t charac terist	Afte age 1 to 2	Aft r ag 1 t 2	N t charac te ist c (any ti e fter 6 m th)	N t haracte i t c
S blings ofte ff ted	Yes	N	O cas lly	No	?	No
P o i b east development and menstru at on	No	Rarely (Refs 96 9)	Yes	Yes	N	O e-fourth f ases (Ref 63)
Obes ty	N	N	No	May ccur	No	Y s
Ult m te d g f h t n (m le x hai cl to s)	Seve e	Se e e	No e	N e	N e	V able
U ogenital sinus	P es t	Abs t	Ab t	Absent	Abse t	Absent
Hypertensio	Som t m	No	N	N	No	Yes
Statural dev lopment and bo e ge	Ad d	Ad a d	Ad d	Adva ced	Sl ghtly d va c d	Often tard d
Salt-los g d r li uffi e e cy	Occ rs b t l c mmon th n m l	N	No	N	N	No
17 K tost d t	El ted—m y e ce d d lt l	Ele ted—m y eed ad lt mal	N mal sl ghtly h gh fo g b t not abov dult m l	Pre umal ly me as p e ding col um	N mal but slightly above er age f age	Ad al hype plas n al to slightly le ated Ad enal ade n ma o mal Adr nal a ce may be y high but c be o mal
Eff ct f orti so (CXVI) 1 KS et on	Sharp d as	N e	P esum bly de c ase †	P mably a d as †	P e mably de c ease †	Fall w th hype plas † N ch g ith t m ?
The py	C rtis (CXVI) (alt d DOCA f nd ated)	E c i	N e	Surge y ly cessful	No e	E ise tumo I hyperplas adiate p tui tary o ad e lectomy
P g os as to l fe e pe ta y ith p ope t tment	Good	D pe d mal g y f t mo	Good	Poo f d to t m	Good	Good f ad l d n ma s essfully e moved Pr b ably good th d e l ctomy f hype plas

An admixture f f tures of Cushing s sy dr m and v lism is not e La ting in these col mns ar l as d th pure form of h.

† Small doses of ortiso e (CXVI) ed 17 k toste d t n ormal bj cts (ad l pp ess)

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CHAPTER

17

Androgen Deficiency —Hypogonadism

Definition of Hypogonadism

The term hypogonadism, as commonly employed in the male denotes deficient secretion of male hormone by the testes The complete and permanent loss of hormone which follows castration before puberty produces the typical clinical picture of the eunuch Characteristic features include a peculiar body habitus in addition to absence of secondary sex characteristics There is a spontaneous form of hypogonadism termed eunuchoidism in which the deficiency may be equally complete Intermediate grades of hypofunction also occur The clinical features of hypoandrogenism are much less striking if the loss of hormone *is* delayed until after the attainment of normal sexual maturity Postpuberal hypogonadism is discussed separately in the latter part of this chapter

Before eunuchoidism is considered brief mention will be made of the possible clinical significance of androgen deficiency due to adrenal failure and note will be taken of testicular disorders characterized by serious impairment of gametogenic function

Significance of Adrenal Androgens

In previous chapters it has been pointed out that androgens are elaborated both by the testis and the adrenal cortex In fact a larger proportion of the androgenic material found in male urine arises from the adrenal than from the testis and in the female essentially all of it is from the adrenal For this reason one might suspect the existence of clinically manifest androgen deficiency due to adrenal failure In Addison s disease for example 17 ketosteroid excretion in the male may fall to levels even below those seen after castration and in the female the output approaches zero Surprisingly enough the clinical

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Another is the tubular degeneration which occurs postpuberally in the undescended testis due presumably to the abnormally warm environment of the ectopic position Leydig cell structure and androgen



Fig 1 Testis biopsy in Klinefelter's syndrome Testicular biopsy in a 58 year old man with Klinefelter's syndrome All tubules show complete degeneration Although scattered nests of Leydig cells are present his clinical status indicates that their function is deficient Gynecomastia appeared shortly after puberty Potency was lost at the age of 20 followed by decreased muscle mass cutaneous pallor and female distribution of subcutaneous fat

elaboration are fairly well preserved in the undescended gland[2] That the resistance of the Leydig cells to the stress of abnormal environment is not always complete is suggested by reports of evidence of impairment in their structure and function when the gland remains undescended for a prolonged period[3,4]

consequences are not striking Although an occasional woman with Addison s disease will suffer loss of pubic and axillary hair [1] in men there is no significant alteration of secondary sex structures It was once suspected that the residuum of asthenia encountered in Addi son s disease which was seen particularly in women who in other respects were well controlled with desoxycorticosterone (CXXI) might be due to a need for anabolic support normally supplied by adrenal androgen Opinion is divided however as to whether a sup plement of testosterone is beneficial in such cases Moreover now that cortisone is available the control of all clinical symptoms is usu ally achieved with ease

It is quite clear that in adrenal insufficiency the loss of corticoid hormones leads to a far more serious physiological derangement than does the withdrawal of adrenal androgens Even though the adrenals secrete much steroid material which is androgenic or is degraded to metabolites with androgenic activity the potency of these end products is not great when compared to that of testosterone secreted by the testis (see Table 1) In the female the adrenal androgens appear to

TABLE 1

THE SYSTEMIC EFFECTS OF ANDROGENS CONTRIBUTED BY THE GONADS AND THE ADRENAL CORTEX

	Adrenal Androgens	Gonadal Androgen
Men	Subnormal growth of pubic and axil lary hair	(Testis) Promotes full growth of penis accessory sex glands facial and body hair somatic muscles
Women	Normal growth (feminine type) pubic and axil lary hair	(Ovary) Output of androgen minimal and of uncertain sig nificance

be concerned with the growth of pubic and axillary hair but no other vital function has been clearly established

Disorders Dominated by Tubular Failure

It is well known that sterility due to disease of the testicular tubules may occur without deficiency of androgen secretion In some instances the tubules may have suffered damage but the androgen secreting Leydig cells remain relatively well preserved because of their greater resistance to injurious stress An example of the selective destruc tion of tubular epithelium is the sterility produced by irradiation

pute[8] It has been postulated that the hormone whatever its nature arises from the Sertoli cells One line of evidence consists of a reported failure to find increased gonadotropin excretion in cases of seminiferous failure unless the Sertoli elements also are destroyed[9, 10] McCullagh[11] and Heller and co workers[12] on the contrary have questioned this conclusion because of their frequent encounter with patients who suffered destructive tubular lesions not involving the Sertoli cells but who nevertheless still excreted increased amounts of gonadotropin

Causes of Eunuchoidism

Secondary to pituitary deficiency

In a series of 148 eunuchoidal men mentioned by Nelson[13] the disorder was traceable to the pituitary in 62 per cent Albert et al found the percentage to be 20 to 25 in a smaller series of cases[80] The testes of these patients are infantile in size and the histological features usually are similar to those of the normal prepuberal gland Sertoli cells remain undifferentiated the development of germinal cells is arrested and mature Leydig cells are absent It is generally believed that the growth of testicular tubules is under the control of a particular gonadotropin from the anterior pituitary which in the female stimulates the ovarian follicle (FSH) whereas the Leydig cells are stimulated by the luteinizing hormone (LH ICSH) The changes in the testis are compatible with a primary deficiency of both these gonadotropins One might conceive of a more complicated chain of events in which the primary defect is in FSH This would lead to tubular failure and therefore decreased X hormone If X hormone resembles estrogen the end result might be a diminution in the output of LH because secretion of the latter is known to be enhanced by estrogen[10] It is not likely that the original defect is solely in LH which then theoretically could lead to Leydig cell failure and finally tubular failure secondary to androgen deficiency (see Chapter 11) That a real deficiency of FSH exists is evidenced by the low excretion of urinary gonadotropin as determined by the standard assay method This test depends upon the presence of a large proportion of FSH for genital stimulation of the female mouse

Proof that a case of eunuchoidism is due to deficient gonadotropin production is achieved by demonstration of a low titer (or at least not a high titer) of gonadotropin in the urine with confirmatory evidence obtained by testicular biopsy or by a positive therapeutic trial with

Simple pure defects in spermatogenesis leading to infertility are of common occurrence. Because simple sterility in itself is not usually termed hypogonadism the subject is not considered in detail. A condition known as Klinefelter's syndrome nevertheless deserves special mention at this point in addition to its subsequent discussion under eunuchoidism. In this disorder there is severe tubular degeneration, peritubular fibrosis (Fig 1), aspermia and often an unexplained gynecomastia (Fig 2).[5,6] It should be noted that selective tubular destruction and gynecomastia have been described in patients with leprosy.[79] Although some patients with Klinefelter's syndrome suffer from varying degrees of Leydig cell failure (undeveloped secondary sex characteristics and low 17-ketosteroid excretion) others are well masculinized and the Leydig cells appear to be intact. Of interest is the abnormally high output of gonadotropin even when the testes are secreting normal quantities of androgen. It would seem that such a syndrome is associated with primary tubular failure and that the loss of some pituitary inhibiting hormone normally arising from a source other than Leydig cells accounts for the hypersecretion of gonadotropin. Suspicion exists that the inhibiting hormone ("X hormone" or "inhibin")[77] is an estrogen. However, even though estrogen has actually been isolated from the testis,[7] its cell of origin is in dis

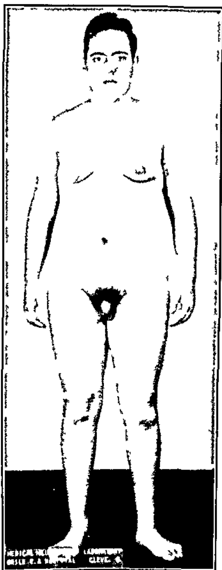


Fig 2. Klinefelter's syndrome in an 18 year old boy. Although the penis and sexual hair are well developed the testes are but 1½ cm long. Aspermia and gynecomastia are present. Gonadotropin excretion is elevated. He as yet shows no features of androgen deficiency.

"KLINEFELTER S SYNDROME" "PUBERAL FAILURE The severe tubular failure which dominates this syndrome has already been discussed Leydig cells are nearly always present In many instances however eunuchoid features are in evidence Moreover careful cytological study shows the Leydig cells in most cases to be abnormal in their appearance and in staining characteristics[14] The degree of eunuchoidism is often mild but in some examples approaches the severe form It would seem that this syndrome is congenital in origin that it becomes manifest at about the time of puberty and that the degree of eunuchoidism varies not only with the severity of Leydig cell involvement but also inversely with the degree of puberal development attained before the Leydig cells suffer functional impairment

Diagnostic criteria of the disorder include azoospermia with high gonadotropin excretion and a testicular biopsy showing tubular changes varying from early degeneration to complete hyalinization Leydig cells are present but are not entirely normal in appearance The testes grossly are usually 1 to 1½ cm in length and are fairly firm Gynecomastia is often present and tends somewhat to vary inversely with the degree of eunuchoidism The enlargement of the breasts is due to proliferation of both the stromal elements and ducts The cause of the gynecomastia is conjectural

The undescended testes encountered in male pseudohermaphroditism may exhibit severe tubular hyalinization[25] Other features resembling Klinefelter s syndrome are high gonadotropin excretion the appearance of male secondary sex features at puberty and frequently gynecomastia

PREPUBERAL AGENESIS "FUNCTIONAL CASTRATION" In this disorder it may be impossible to identify any recognizable testicular tissue grossly or microscopically The testis either fails to develop or suffers severe atrophy early in life[10 15] A mistaken diagnosis of undescended testes is sometimes made Puberty never appears and eunuchoidism is severe Because of the absence of inhibiting testicular hormones which normally suppress the pituitary gonadotropin excretion is high Diagnosis is established by the latter finding along with the failure to establish any antecedent local disease which could have destroyed the gonads

MISCELLANEOUS DISORDERS Occasional cases are encountered wherein severe testicular atrophy has followed surgical procedures such as orchiopexy Some degree of ischemic damage to the gland after this operation is probably more common than realized Severe trauma or infections are not common causes of bilateral atrophy Mumps orchi

chorionic gonadotropin It has been reported that these patients as opposed to cases of primary testicular failure exhibit a moderate rise in 17 ketosteroids [73, 74] and a sharp increment in estrogen excretion [74] during the administration of chorionic gonadotropin

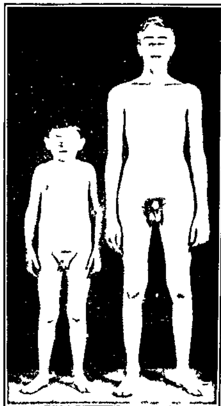


Fig 3 A 17 year old pituitary dwarf posed with a normal 17 year old boy to show short stature and sexual infantilism Gonadotropins were less than 2 mouse uterine units per 24 hours Bone age 7 years

The pituitary gland in many cases under discussion will show no evidence of impairment of other functions nor will any indication of an organic lesion in or near the sella be apparent In such instances a selective functional defect appears to exist Some of these patients represent simple delayed puberty and eventually develop normally without therapy At times the deficiency may involve other pituitary secretions such as the growth hormone In this syndrome genital development is arrested and secondary sex characteristics are absent but there is dwarfing rather than the normal or elongated stature of simple eunuchoidism (Fig 3) The sexual infantilism with retarded growth often encountered in debilitated poorly nourished or chronically ill children is probably due to a reversible functional depression of the pituitary which is secondary to the illness Organic lesions such as craniopharyngioma may at first produce only hypogonadism but eventually can result in a serious loss of many pituitary functions Such lesions should be ruled out in all cases of hypogonadotropic hypogonadism by careful clinical and roentgen studies

Primary testicular disease

Thirty eight per cent of Nelson s series of eunuchoids suffered from primary disease of the testes Several subcategories have been recognized

normal No beard and a high pitched voice are due in all likelihood to end organ resistance within these particular structures

Froelich's syndrome

Froelich's syndrome also known as adiposogenital dystrophy deserves special comment This designation is usually applied to a boy approaching adolescence who shows obesity which is most marked over the trunk hips and thighs There may be genu valgum The genitalia are judged to be small for the boy's age

One finds statements in the older literature that the obesity is due either to gonadal or pituitary failure There is to the contrary no evidence that either the gonads or pituitary are implicated in the production of the adiposity Bruch[28] has reviewed the original publications dealing with the case described by Froelich in 1901 The boy had clear cut evidence of an intracranial tumor along with hypogonadism and a rapidly developing obesity Froelich made a correct preoperative diagnosis of a tumor involving the hypophysis His conclusion was based on the findings in a number of autopsy reports which described hypogenitalism and obesity in cases of tumor in this region The erroneous concept of "pituitary obesity" had its origin with this case However as early as 1904 Erdheim pointed out that obesity did not occur unless a tumor of the pituitary invaded the surrounding hypothalamic region and moreover that obesity could occur with tumors of the brain which did not involve the gland Subsequent experimental work on animals by many workers has borne out Erdheim's contention that hypothalamic injury may produce obesity but destruction of the pituitary per se does not.

An endocrinologist dislikes to use the term Froelich's syndrome but it is widely applied to fat boys with small genitalia no matter what the etiology might be A great number of these patients are nothing more than fat and the penis is not as small as it seems but is simply hidden in a deep pad of surrounding fat. In other instances an actual delay in puberal development may exist (Fig 4) Perhaps in such a circumstance there is a combined dysfunction of the anterior pituitary and hypothalamus The disorder however is almost always functional in nature and sexual development usually appears spontaneously by the age of 16 [7] It is indeed rare to discover a tumor involving the hypothalamus and hypophysis as described by Froelich

Although fat boys with truly retarded genital development frequently show low levels of pituitary gonadotropin in the urine McCullagh has found that some of them excrete abnormally high quantities of this hormone and exhibit hypoplasia or atrophy of testicular ele

tis although often destructive to tubular elements usually spares the Leydig cells and hence is not a likely cause of eunuchoidism

Less common types

Some degree of hypogonadism is commonly encountered in the Lawrence Moon Biedl syndrome The low output of gonadotropin demonstrated in several cases suggests a pituitary defect [16] however primary testicular failure apparently may occur [17] Werner s syndrome myotonia dystrophica and similar hereditary disorders are frequently accompanied by testicular atrophy [18] In myotonic dystrophy since the Leydig cells are little affected frank eunuchoidism does not occur however the tubules may undergo severe atrophy and gonadotropin secretion may be elevated [10 19–21] Turner s syndrome in the male with testicular degeneration has been described [2 23 82] In all the above hereditary syndromes the gonadal deficiency is not the cause of the multiple somatic defects but is simply another of the numerous manifestations of the genetic aberration

Several cases of eunuchoidism associated with hypoplasia of the Leydig cells but with relatively intact gametogenic function have been reported [10 4 8] Owing to the normal tubular mass the testes may not be small *Because of inadequate seminal fluid to transport sperm* fertility may be impaired The excretion of 17 ketosteroids tends to be low whereas that of gonadotropin is normal In that the standard bioassay for gonadotropin depends principally on the presence of FSH it is still possible that the Leydig cell failure is due to deficient LH production Evidence that such is the case is the positive clinical response which follows treatment with chorionic gonadotropin This disorder is of particular physiological interest because of (1) the apparent existence of a selective deficiency in LH (2) the preservation of gametogenic function in the absence of normal amounts of androgen (3) the failure of androgen deficiency per se to bring about hypersecretion of pituitary gonadotropin

A striking form of male pseudohermaphroditism has been described wherein the testes are located in the pelvis and contain tubules Sertoli cells and Leydig cells but appear to secrete estrogen rather than androgen [8 81] Spermatogenesis is absent The body habitus and psyche are strictly feminine and breasts are well developed On the other hand the uterus and tubes are rudimentary and menses are absent A peculiar characteristic is the absence of pubic and axillary hair

A type of "pseudo eunuchoidism" has been encountered which fails to respond to androgen therapy [3] Testicular function is actually

the time of expected puberty Before this time there is no significant elaboration of androgen even by the normal gland The need for caution in the interpretation of small genitalia in prepuberal boys has been emphasized in Chapter 15

If secretion of testicular androgen does not appear at the age of normal puberty the diagnosis of eunuchoidism becomes readily apparent not only by virtue of the failure in genital growth but also because of a characteristic body habitus and facies which often identify the disorder at a glance Hamilton has made extensive clinical observations on castrate men and has directed attention to the diverse affects of androgen on a variety of nonsexual organs[9,10] Additional references pertaining to the characteristic features of eunuchoidism may be found in Chapter 18

BONE DEVELOPMENT In most instances but not invariably the stature is above average because of a disproportionate increase in length of the long bones (Fig 5) A quantitative estimate of this distortion of growth may be derived from several measurements The arm span instead of being approximately equal to standing height as in the normal boy may exceed the height by several inches Increased leg length may be demonstrated by measurement of the distance from the pubis to the floor in the standing position This normally is about equal to that from the pubis to the vertex but in eunuchoidism it is excessively great The ratio of standing to sitting height likewise is excessive

The lengthening of long bones is ascribable to a delay in epiphyseal closure with consequent prolongation of the period of active growth In the normal boy at puberty closure is hastened by androgen hence further growth is prevented The epiphyses of the radius and ulna although behind their schedule of union do eventually unite Those of the crest of the ilium appear to remain open indefinitely In middle age osteoporosis kyphosis and joint deformities are sometimes encountered

MUSCLES Muscular development and strength are relatively poor compared to the normal adult male Animal experiments indicate that the shrinkage in size of the muscles is the result of atrophy of individual fibers rather than disappearance of cell units

FAT In physical appearance the eunuch may vary from slender to markedly obese In most instances there is a distinct suggestion of obesity because of prominent fat deposits about the hips buttocks breast region and abdominal wall Nevertheless it is surprising that body weight, as shown by statistical studies is on the average somewhat less than that of the expected normal This disparity is explained by the relatively severe deficit of muscle mass which offsets

ments [8] Although this would suggest that the testicular hypofunction is not always secondary to pituitary inadequacy but may sometimes be primary it is of interest that sexual stimulation was achieved with chorionic gonadotropin

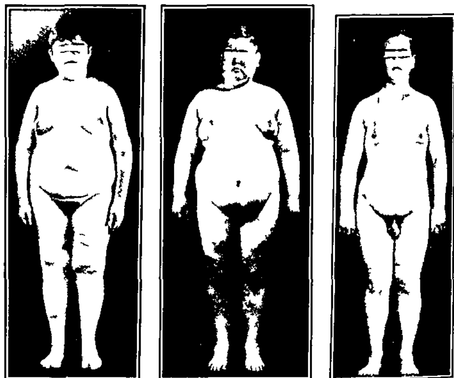


Fig 4 A 27 year-old boy on the left who had been followed since the age of 17 because of obesity and failure of sexual development Bone age 17 years Gonadotropin excretion less than 2 mouse uterine units 17 ketosteroid excretion 12 mg X ray showed nothing in region of sella Patient refused treatment This is an example of adiposogenital dystrophy i e hypogonadotropic hypogonadism and obesity in which spontaneous sex development failed to occur The patient at age 16 in the center shows obesity and retarded sexual development Penis 2 cm long Bone age 13 years Gonadotropin excretion less than 2 mouse uterine units No specific treatment was given On the right he is shown at the age of 20 with normal masculinization and testes 5 cm long This is an example of obesity and delayed puberty a type of Froelich s syndrome which disappeared spontaneously except for some persistent obesity

Clinical Features of Male Hypogonadism

Prepuberal onset

Although serious testicular atrophy may exist in the early years of life the physiological consequences do not become manifest until

the time of expected puberty Before this time there is no significant elaboration of androgen even by the normal gland The need for caution in the interpretation of small genitalia in prepuberal boys has been emphasized in Chapter 15

If secretion of testicular androgen does not appear at the age of normal puberty the diagnosis of eunuchoidism becomes readily apparent not only by virtue of the failure in genital growth but also because of a characteristic body habitus and facies which often identify the disorder at a glance Hamilton has made extensive clinical observations on castrate men and has directed attention to the diverse affects of androgen on a variety of nonsexual organs [9,30] Additional references pertaining to the characteristic features of eunuchoidism may be found in Chapter 18

BONE DEVELOPMENT In most instances but not invariably the stature is above average because of a disproportionate increase in length of the long bones (Fig 5) A quantitative estimate of this distortion of growth may be derived from several measurements The arm span instead of being approximately equal to standing height as in the normal boy may exceed the height by several inches Increased leg length may be demonstrated by measurement of the distance from the pubis to the floor in the standing position This normally is about equal to that from the pubis to the vertex but in eunuchoidism it is excessively great The ratio of standing to sitting height likewise is excessive

The lengthening of long bones is ascribable to a delay in epiphyseal closure with consequent prolongation of the period of active growth In the normal boy at puberty closure is hastened by androgen hence further growth is prevented The epiphyses of the radius and ulna although behind their schedule of union do eventually unite Those of the crest of the ilium appear to remain open indefinitely In middle age osteoporosis kyphosis and joint deformities are sometimes encountered

MUSCLES Muscular development and strength are relatively poor compared to the normal adult male Animal experiments indicate that the shrinkage in size of the muscles is the result of atrophy of individual fibers rather than disappearance of cell units

FAT In physical appearance the eunuch may vary from slender to markedly obese In most instances there is a distinct suggestion of obesity because of prominent fat deposits about the hips buttocks breast region and abdominal wall Nevertheless it is surprising that body weight as shown by statistical studies is on the average somewhat less than that of the expected normal This disparity is explained by the relatively severe deficit of muscle mass which offsets

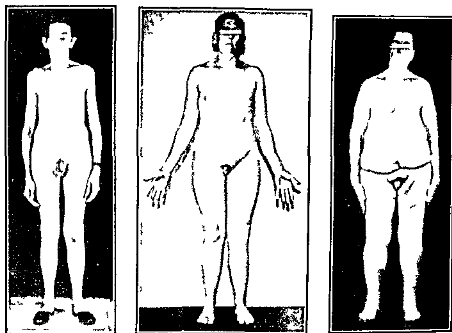


Fig 5 Eunuchoidism On the left a 50 year old man with hypogonadotropic eunuchoidism showing typical elongation of extremities small penis and scanty pubic hair Voice was high pitched beard absent testes 0 5 cm long and gonadotropin excretion less than 4 mouse uterine units In the center a 37 year old subject with primary testicular failure (gonadotropin 128 mouse uterine units) Spermatic structures and a small knot of irregular tissue could be palpated in the scrotum but no testicles could be felt This is undoubtedly a case of primary testicular agenesis Muscular development is poor breasts are prominent and subcutaneous fat distribution is of the feminine type On the right a case of the Lawrence Moon Biedl syndrome in a 49 year old man with severe testicular atrophy Gonadotropins were less than 4 mouse uterine units Retinitis and nystagmus were present (See reference 16 pt W C)

the gain in fatty tissue The excessive ratio of fat to more solid tissue is clearly illustrated by the low specific gravity of the body even in non obese eunuchs

SKIN The skin everywhere is pallid and pasty in appearance Pallor is due both to poor filling of skin capillaries and to a subnormal content of melanin The lack of melanin is particularly apparent over the penis scrotum and circum anal region These areas would normally appear much darker than the surrounding skin Changes in the physical properties of the skin are evidenced by increased distensibility as determined by quantitative procedures along with a tendency for the face to develop a characteristic wrinkled appearance The wrinkles are not of the coarse variety associated with the loose skin of



Fig 6 Close up of the face of a hypogonadal patient This 63-year-old man suffered severe testicular atrophy following herniorrhophy at age 20 Note the abundant cross hatched wrinkling superimposed upon the coarser wrinkles which are incident to the aging process His beard grew sparse but was never completely lost.

senility but are fine and very abundant (Fig 6) Typical wrinkling may appear in young hypogonadal subjects even before the age of 30

The sebaceous glands remain inactive For this reason the consequences of an oily skin with comedo formation and acne so typical of normal adolescence are not encountered The merocrine and apocrine glands of the axilla are poorly developed Hence there is less sweating and less odor in this region than would normally be present

The subcutaneous veins of the forearm are relatively inconspicuous and of delicate texture

HAIR Growth of the adult beard is entirely lacking in the hypogonadal subject Other areas which fail to develop coarse pigmented

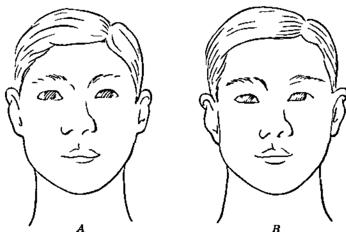


Fig 7 Tracing of the hair line from photographs of a patient with eunuchoidism before (left) and after (right) 3 years of treatment with methyl testosterone Note the development of lateral recession

hair of normal length are the extremities chest lower abdomen scrotum and perianal region The shafts remain thin straight poorly pigmented and retain the appearance of fine sparse down as seen in the juvenile state Pubic and axillary hair on the other hand are not completely absent in simple testicular failure Adrenal androgens are sufficiently potent to stimulate considerable development in these two regions The growth over the pubis resembles that of the female The pattern is small and the upper border horizontal Axillary hair tends to be sparse but is not completely absent In panhypopituitarism adrenal and testicular androgens are both deficient hence these areas are more completely devoid of hair than in simple hypogonadism

The hair of the scalp is somewhat fine in texture and the frontal border appears as an uninterrupted curve without the usual wedge shaped indentations which are present over the sides of the forehead in the normal adult (Fig 7) Extensive simple baldness does not occur The production of baldness in some patients by therapy with testosterone indicates that this hormone actually suppresses hair growth in susceptible areas of the scalp provided that the genetic factor for baldness is present

VOICE The voice retains its juvenile high pitch because of failure of the larynx to enlarge and of the vocal cords to lengthen The Adam's apple remains inconspicuous

GENITALIA The testicular changes have been described in preceding sections The scrotum is of relatively small capacity and is non pendulous The penis retains the small caliber and length of an immature boy's Erectile potency is quite variable In most cases erections are infrequent and turgidity tends to be inadequate Often the erectile power is completely absent At the other extreme are those hypogonadal patients who are able to perform satisfactory coitus with orgasm even though seminal emission is absent or scanty The prostate seminal vesicles and epididymis are atrophic

PSYCHIATRIC ASPECTS Psychiatric disorders are common Many patients tend to be seclusive submissive insecure emotionally unstable and suffer from a constant undertone of anxiety In some instances there is overcompensation in the form of excessive aggressiveness Such psychologic derangements however might not be due to hormone deficiency per se but are more probably attributable to the neurotic reaction which one would expect in the presence of such a physical defect The male psyche is perhaps more vulnerable to sexual inferiority than to any other bodily disorder The chiding by male companions during adolescence leaves in the mind a persistent subconscious scar and the emotional trauma of being mistaken for a woman during telephone conversations is a constant reminder that all is not right Whether the male hormone also exerts a specific direct effect on attitude and behavior in *man* is a difficult question The importance of such a role has been minimized in the human subject[81, 3]

Feeble mindedness epilepsy and insanity are not caused by male hormone deficiency Such claims in the older literature were undoubtedly based on reports of persons suffering from a complex constitutional disorder to which the genital defect was secondary The mental capacity of the eunuchoid individual varies within the same range as that of the general population and intellectual brilliance is by no means precluded

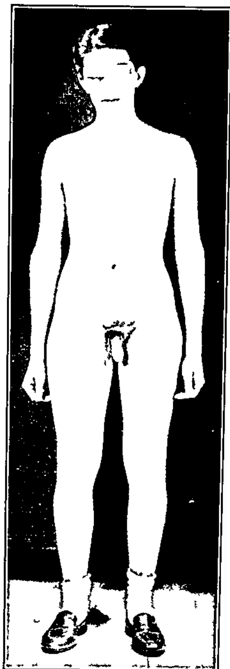


Fig 8 Incomplete hypogonadism age 24 One testis undescended the other 1 cm long Gonadotropin excretion 128 mouse uterine units Although the penis was enlarged and well pigmented and sexual potency present the prostate was small and seminal fluid scanty without sperm Voice was high pitched and a very slight beard was present on upper lip and chin Although gynecomastia was absent this case may represent a variant of Klinefelter s syndrome

Contrary to popular notion the hypogonadal man is not homosexual This misconception leads to social rejection and to frequent solicitations by true homosexuals who are misled by the patient's lack of masculinity These patients very often show a distinct sex interest in girls but its expression may be thwarted by self consciousness arising from the genital hypoplasia Some of them however find a sympathetic mate marry, and occasionally indulge in a sex life which is not so unsatisfactory as might be supposed

MISCELLANEOUS CHANGES The basal metabolism averages about 10 per cent below normal Although serious anemia does not occur the red count tends to be somewhat below 5 million the hematocrit is somewhat depressed and hemoglobin values are in the range of 13 5 to 14 grams rather than 15 [29, 33] Sedimentation rate averages higher than that of normal males and there is a relative increase in the fragility of erythrocytes Creatinuria is observed in some cases [34] but is not of invariable occurrence

Excretion of 17 ketosteroids is reduced (Chapter 20) and the output of estrogen likewise is low [33]

INCOMPLETE HYPOGONADISM The manifestations of eunuchoidism may not always be present in complete form Incomplete types arise if puberal changes have already begun before the testis fails or if the degree of testicular failure is only partial Facial hair because of its dependence on high levels of androgen is invariably deficient even in the milder forms of eunuchoidism Penile scrotal and prostatic development will sometimes progress to a moderate extent if the secretory function of the testis is reduced but not completely abolished (Fig 8) It should be emphasized that the relative abundance of body hair genital size and the pitch of the voice are all subject to constitutional factors which impose certain limitations in normal men irrespective of an adequate supply of androgen

Postpuberal onset

CASTRATION If orchectomy is performed after the attainment of sexual maturity the ensuing changes are often not particularly conspicuous on casual examination [36] The voice remains deep and the beard is fairly well retained Body hair does not regress rapidly but may slowly become less plentiful and less coarse The penis does not shrink greatly in size Power of erection varies as does the preservation of sexual desire [37] In general it is fair to say that both tend to decrease and may disappear entirely although in some instances sex interest and erectile function are reasonably well maintained [38, 39]

Changes in fat distribution and in the specific gravity of the body (decreased ratio of muscle mass to fat) are demonstrable as are the hematologic and metabolic alterations described in the preceding section The prostate gland and seminal vesicles become extremely atrophic Gonadotropin excretion rises Hot flashes are more commonly encountered in the postpuberal castrate than in the prepuberal type, presumably because of the abrupt and complete withdrawal of hormone Physical strength and endurance may be impaired and frequently there are complaints of nervous tension and emotional instability but a severe neurotic reaction is uncommon

SPONTANEOUS TESTICULAR FAILURE IN LATE LIFE The "male climacteric has been a subject of considerable controversy The introduction of testosterone (VIII) for general clinical use was followed by misgivings among the conservative elements of the medical profession lest the hormone be exploited for supposed powers of rejuvenation Does testicular function decline with age and give rise to a male climacteric? If so how frequently is it encountered and how may it be diagnosed?

As far as spermatogenesis is concerned there is abundant evidence that even in advanced senility the testis does not inevitably suffer a fate comparable to that of the ovary Tubular degeneration does occur frequently as old age approaches and yet in about half the cases studied between the ages of 70 and 90 sperm formation has been demonstrated histologically[40] Whether Leydig cell function is affected by age is a much more elusive question The lack of any cyclic end organ response to androgen in the male which can compare with menstruation as an indicator of ovarian hormone production in the female presents a problem with no easy solution

In searching for an answer one might review such evidence as is offered by the histological appearance of the testis or the anatomic status of an organ such as the prostate which depends on androgen for its integrity Hormone assays the character of the symptoms known to occur after androgen withdrawal and the effect of specific therapy on the latter symptoms may provide suggestive evidence

Histological examination of the senile testis affords no answer There is increased pigmentation of Leydig cells but no frank degeneration or atrophy[40] That cell function could be impaired however without severe morphological change remains as a distinct possibility

After castration the prostate undergoes extreme atrophy but in old age there is no gross decrease in size of the gland Not only is the opposite generally true but it is of interest that prostatic enlargement has been described in patients thought to be suffering from the

male climacteric [41] But in spite of a tendency for the senile gland to be large there is *histologic* evidence of atrophy The atrophic change develops gradually and is nonuniform throughout the gland Moore [42] *considered this involution to stem from a decline in hormone produc* tion by the testis and stated that the spottiness of distribution might be due to regional variations in tissue reactivity combined with a fluc tuating supply of hormone In opposition to this view it could be argued that the spottiness is more consistent with patchy vascular degeneration Moreover Moore and McClellan in later studies were unable to institute repair of the presenile prostate with male hormone [43] The retrogression of prostatic carcinoma after orchectomy in older men indicates that at least in these patients testicular hormone had previously been present in significant amount Perhaps in the con siderable number of individuals who harbor microscopic prostatic car cinomata which never progress the neoplasia has been held in abey ance by poor testicular function and yet other plausible hypotheses can readily be formulated

As judged by the acid phosphatase content of prostatic fluid meas ured either directly [44] or by assays on urine [45] the ability of the gland to secrete this enzyme declines in later life Whether such a decline should be ascribed to an insufficient supply of androgen or to an in trinsic degeneration of the prostate is uncertain

The excretion of androgens and 17 ketosteroids in human urine is reduced after castration (Chapter 20) Likewise these compounds are excreted in progressively decreased quantities as senility ap proaches Unfortunately these two observations do not provide prem ises for a deduction since fluctuations in excretion are dependent on androgens from both the adrenal and the testis Nevertheless it might be reasoned that although a low output of urinary androgen in senility does not necessarily denote testicular hypofunction yet it suggests a decline in the over all production of androgens within the body and thus hormone therapy in the aged subject might be of benefit as a "tonic" Although the test of such a theory would involve well-con trolled clinical trials such reasoning in itself gives scant justification for enthusiasm Witness the decline in basal metabolism with age There is no general agreement that senility is an indication for thyroid replacement therapy

An assay of urinary gonadotropin might yield certain information inasmuch as the output is increased in the presence of testicular fail ure but not with adrenal cortical failure Studies of gonadotropin excretion in middle aged or old men have shown an increased output in only a fifth to a third of the cases as compared to approximately

80 per cent of reported postmenopausal women[46-48, 75] The conclusion is therefore justified that a primary testicular failure capable of affecting gonadotropin excretion is not the rule in older men The significance of the high levels encountered in a minority of instances is uncertain We have performed assays on nine men of this age group who presented symptoms compatible with the climacteric syndrome as described by Werner[49] Values were high in five Heller[50] McCullagh[51] and Goldzieher and Goldzieher[75] in larger groups of similar patients have reported an increased incidence of elevated values Nevertheless it is not justifiable to assume that gonadotropin excretion is a specific diagnostic index of testicular androgen deficiency It must be remembered that tubular failure alone affects gonadotropin excretion Moreover in the series of Heller and Shipley[5] of the seven out of thirty five unselected old men who excreted excessive amounts only one had complained of symptoms considered to be compatible with such a syndrome

Is the symptom complex sufficiently characteristic to establish a clinical diagnosis? There is a popular belief among both the profession and the laity that impotence and loss of sex desire are specific signs of testicular failure It has been pointed out above however that desire and power of erection are not necessarily abolished by castration Moreover there is no doubt that psychogenic factors are of paramount importance in sexual performance and interest This is not to say that androgens do not have an important supportive effect on these functions but it should be remembered that the controlling mechanism is complex and that androgen secretion is only one of the factors involved in the process The common loss of sex interest and failure of erectile power in late life although consistent with hormone deficiency could well be due to independent psychosomatic or neuromuscular alterations

Vasomotor symptoms along with nervous instability are common at the menopause in women Thus it has been reasoned that testicular failure in later life might produce similar phenomena Castration in the adult male is in fact commonly followed by hot flashes This symptom must therefore be accorded considerable weight in suspected cases but it is not a specific indicator of androgen deficiency Flashes are occasionally encountered in simple emotional and psychiatric disorders Symptoms reputedly due to the male climacteric such as irritability anxiety insomnia poor memory dizziness fatigability melancholia lack of pep and interest and feelings of futility are certainly quite compatible with a purely nervous or emotional derangement which could exist as a primary disorder unrelated to the endocrine

status of the patient Severe neuroses or psychotic reactions are not the rule after adult castration and hence the more marked the nervous symptoms the more likely it is that the problem is primarily psychiatric.

A therapeutic trial with male hormone in suspected cases has much in its favor as a diagnostic approach (Chapter 18) In fact the response to specific therapy is the mainstay of proof of diagnosis in most cases of male climacteric which have been reported[41,49,53] Only occasionally however have clinical trials been controlled for the possible effect of suggestion The hazard of neurotic dependence must be faced in any therapeutic trial of this nature

The conclusion seems justified that androgen deficiency such as in hypogonadism is by no means an inevitable consequence of the aging process In some individuals however it probably does occur For want of controlled statistical studies its degree of prevalence cannot at present be estimated It is apparent from the foregoing discussion that a diagnosis cannot usually be made with ease The diagnosis may be suggested when a man in middle or late life presents himself with complaints of fatigability impotence and nervousness The suspicion is somewhat stronger if he has never previously experienced these symptoms and environmental sources of emotional strain or conflict are absent The occurrence of hot flashes along with elevated urinary gonadotropin would strengthen one s suspicion even further but the simplest and most conclusive proof is probably from a good therapeutic response to male hormone *but no benefit from placebo medication*

HYPOPITUITARISM A destructive lesion such as a chromophobe tumor craniopharyngioma or other growth which invades the sella may seriously affect pituitary function Impotence and loss of sex interest are early indications of impaired secretory activity[54,55] Coincident with signs of declining sex function are shrinkage in size of the testes along with a decline or disappearance of gonadotropin in the urine Histologically the testes in this circumstance may show severe atrophy of both tubular elements and Leydig cells[56] If the anterior pituitary gland is progressively destroyed evidence of thyroid and adrenal insufficiency may also become clearly apparent 17 Ketosteroids while somewhat low if the gonads alone are affected reach very low values when the destructive process leads to secondary atrophy of the adrenal glands

The testicular atrophy which is sometimes observed in hepatic cirrhosis could be related to a functional suppression of the anterior pituitary by an excess of estrogen arising from incomplete hepatic inactivation or excretion[57,59] Simple malnutrition might play a part

In hemochromatosis the mechanism might be similar although direct involvement of the pituitary by the disease is usually demonstrable at autopsy[60] Testicular atrophy accompanied by low gonadotropin excretion and occasionally gynecomastia has been described after severe injury to the spinal cord[61] Seminiferous degeneration has been observed frequently in schizophrenia[62] but Leydig cell failure is not found

Therapeutic Castration

There are several disorders in which the reduction of circulating androgen by castration is beneficial

Cancer of the prostate

Huggins[63] showed that orchectomy was often dramatically effective as a palliative measure in relieving the pain and causing temporary arrest of growth in many cases of metastatic cancer of the prostate Statistical studies[64, 6] indicate that life expectancy is prolonged for an average of 6 months in patients with or without metastases In individual patients the prolongation sometimes is certainly even longer But eventually the cancer adapts itself to the low androgen environment i e loses its androgen dependence and again begins to grow in malignant fashion

The possibility of prolonging life even further by reducing circulating androgens to the lowest possible level has been explored After the effects of orchectomy have worn off bilateral adrenalectomy followed by replacement therapy with cortisone (CXVI) alone or in combination with desoxycorticosterone (CXXI) has been shown to extend the remission in some cases[66, 67] Since cortisone (CXVI) is metabolized in part to androgens this corticoid theoretically is not the ideal steroid for replacement rather corticosterone (CXIX) which does not appear to be converted to androgens would be the steroid of choice Further experience will be required to establish the ultimate usefulness of adrenalectomy

Estrogen therapy (1 to 15 mg of diethylstilbesterol daily) appears to be fully as effective as castration in postponing a fatal outcome but may require 1 to 2 weeks to relieve pain as contrasted with 1 to 2 days after orchectomy Estrogen undoubtedly exerts its effect largely by inducing a functional castration" through suppression of pituitary gonadotropin Nevertheless there is some suggestive evidence that when relapse occurs after castration or vice versa a shift to the alternate form of therapy may again bring about improvement[64] The

fatal outcome appears to be delayed somewhat longer when orchectomy and estrogen therapy are employed in combination

Cancer of the breast

Well marked regression of primary and metastatic lesions in cancer of the male breast is the rule after orchectomy [68, 69] Amelioration and suppression of growth may persist for several years In preliminary trials on a small series of women with metastatic breast cancer bilateral adrenalectomy was followed by remission in approximately half of the cases [67, 70] The patients were either postmenopausal or were subjected to simultaneous oophorectomy It is not clear as to which of the several steroids elaborated by the adrenal might be involved in this phenomenon Both estrogens and androgens decline to very low levels

Other conditions

Instances of an apparent activation of a pigmented nevus into a rapidly growing malignant melanoma at the time of puberty would suggest stimulation by sex hormone Castration in one reported case of metastatic melanoma was without effect.[71] Orchectomy has been performed on sex criminals with rather striking success [7] Crimes such as rape and other violent antisocial acts ceased after castration was performed Removal of the testes for therapeutic purposes in benign hypertrophy of the prostate is discussed in Chapter 18

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CHAPTER

18

Androgen Therapy

Stimulation Therapy

Stimulation therapy is based on the capacity of gonadotropic hormone to excite the Leydig cells of the testis to secrete androgen Success is achieved of course only when Leydig cells are present and are capable of functioning but have failed to do so because of an inadequate secretion of gonadotropic hormone from the pituitary The preparation of choice for this purpose is chorionic gonadotropin from human pregnancy urine Some of the commercial products which are available are known simply as chorionic gonadotropin others are designated by various trade names such as Antuitrin S A P L Follutein Korotrin Pranturon and Pregnyl The doses which have been employed for various purposes vary from 100 I U three times weekly to 750 I U twice daily given by subcutaneous injection Other preparations such as pregnant mare s serum and extracts of the pituitary gland are no more effective and are in fact less desirable in that they may not only produce a foreign protein reaction in some subjects but also tend to lose their efficacy after multiple injections because of the development of immunologic resistance

Hypogonadism

It has been noted in Chapter 17 that some cases of hypogonadism are due to a deficiency of endogenous pituitary gonadotropin (*secondary* or hypogonadotropic hypogonadism) and therefore are amenable to gonadotropin therapy It is well to administer large doses of hormone in these cases Heller[67] advocates a dose of 750 I U twice daily for 4 to 6 weeks however 500 to 1000 I U three times a week is more commonly employed Absence of any genital growth after 1 to 2 months speaks strongly against pituitary failure as a cause of the testicular deficiency In a certain number of instances after a course

of such therapy, or several courses at 6-month intervals sexual development may progress spontaneously without further treatment. Such an end result is thought to be due to an awakened function of the patient's own pituitary gland during the period of therapy. To be sure one cannot say with authority that in such instances sexual maturity would not have occurred ultimately without any therapeutic intervention. This is especially true in the age range of 15 to 16 years when a normal but delayed spontaneous puberty is still a distinct possibility.

If the androgenic function of the testes is not spontaneously maintained after two or more courses of stimulation therapy it may be concluded that the patient's own pituitary is not capable of taking over its normal function. In such event there is little reason to continue with this form of treatment. Instead of stimulation of the testis it is more convenient and economical to circumvent this organ entirely and employ substitution therapy with an androgen. These patients would almost invariably remain sterile even if one chose to maintain them on chorionic gonadotropin since this hormone does not stimulate the tubular epithelium. Although pituitary extracts containing an FSH type of gonadotropin might theoretically promote spermatogenesis in such cases this has not been satisfactorily demonstrated in the human being.

Small genitalia in childhood—delayed puberty

Boys with so called hypogonadism and genital hypoplasia observed at an age well before puberty are considered by some physicians to be candidates for therapy with chorionic gonadotropin. Although there is no doubt that the genital organs of a child may be made to grow by this therapy the justification for such interference is not well established. It should be recalled that all prepuberal boys are normally "hypogonadal" in the sense that testicular function is essentially nonexistent. Genital size in young boys tends to vary within wide limits (Chapter 15). Small size in most instances is simply an expression of a genetically conditioned but normal variation within the range of normal. If the onset of puberty is somewhat later than average a boy at 12 may have genital structures which are no bigger than they were at the age of 3 or 4. This is because genital growth does not keep pace with somatic growth during the prepuberal years and it is only by virtue of a rather abrupt stimulation in the puberal period that genital development finally catches up with body growth.

The point has been made that a boy with small sex organs suffers a serious psychological handicap. Experience would indicate how

CHAPTER

18

Androgen Therapy

Stimulation Therapy

Stimulation therapy is based on the capacity of gonadotropic hormone to excite the Leydig cells of the testis to secrete androgen Success is achieved of course only when Leydig cells are present and are capable of functioning but have failed to do so because of an inadequate secretion of gonadotropic hormone from the pituitary The preparation of choice for this purpose is chorionic gonadotropin from human pregnancy urine Some of the commercial products which are available are known simply as chorionic gonadotropin others are designated by various trade names such as Antuitrin S A P L Follutein Korotrin Pranturon and Pregnyl The doses which have been employed for various purposes vary from 100 I U three times weekly to 750 I U twice daily given by subcutaneous injection Other preparations such as pregnant mare s serum and extracts of the pituitary gland are no more effective and are in fact less desirable in that they may not only produce a foreign protein reaction in some subjects but also tend to lose their efficacy after multiple injections because of the development of immunologic resistance

Hypogonadism

It has been noted in Chapter 17 that some cases of hypogonadism are due to a deficiency of endogenous pituitary gonadotropin (secondary or hypogonadotropic hypogonadism) and therefore are amenable to gonadotropin therapy It is well to administer large doses of hormone in these cases Heller[67] advocates a dose of 750 I U twice daily for 4 to 6 weeks however 500 to 1000 I U three times a week is more commonly employed Absence of any genital growth after 1 to 2 months speaks strongly against pituitary failure as a cause of the testicular deficiency In a certain number of instances after a course

Undescended testes

The proper treatment of cryptorchism has for many years been debated by surgeons. Now the endocrinologist has added his voice to the controversy but has not settled the problem. Various aspects of clinical management have been thoroughly reviewed by Bishop.[54] It cannot be disputed that gonadotropic hormone is capable of promoting descent of the testes in both man and lower animals. In fact it is undoubtedly the chorionic gonadotropin of the human mother which normally initiates the descent of these organs during the last month of intra uterine life. It would appear that the mechanism of descent is dependent largely upon the alteration of surrounding structures by the androgen which is elaborated by the stimulated testis. Androgen given directly as such also will produce descent.[3] Androgen however is not generally employed clinically because growth of the testis itself is not stimulated but may be depressed. Gonadotropin on the contrary tends to stimulate testicular growth.

Should undescended testes be treated and if so how and at what age? The e questions cannot be answered without some consideration of the classification of various types. There is one form of pseudo ectopy common in children which is variously called physiological nondescent retractile testis or migratory testis. In this condition there may be a retraction above the scrotum by an overactive cremasteric muscle but the gland can be made to descend by local application of heat or by gentle manipulation. As the child grows older this condition automatically corrects itself and is certain to disappear at puberty. The high incidence of spontaneous descent of suprascrotal testes (60 to 80 per cent) reported by some observers[68, 71] is undoubtedly dependent on the inclusion of these cases in the series.

Cases of true nondescent may be broken down into two categories. The first type is due to mechanical factors which prevent normal migration. In the second subdivision are cases with no anatomic defect, but in which the hormonal stimulus to descent appears to have been inadequate. The latter type will descend spontaneously at puberty when the testis grows and begins to produce androgen. If gonadotropin is administered before puberty these testes likewise descend by virtue of the artificial stimulation. Thus it is evident that gonadotropin therapy brings down only testes which would ultimately descend spontaneously. In cases of true nondescent i.e. those cases without anatomic abnormality the expectancy of migration either from gonadotropin therapy or at puberty is approximately 20 to 30 per cent.

ever that prepuberal boys are less concerned with their genital proportions than are mature men Moreover an excessive concern of the parents over the child s genital status along with an extended series of shots will not help the child s psychological outlook Behavior problems have actually been thereby precipitated [2]

An attitude of unconcern can be maintained until about the fourteenth year If however no signs of puberal development are in evidence after this age the psychological problems become very real The boy is acutely conscious not only of his retarded sexual status but also of his poor physical development since he has not had the advantage of the growth spurt which normally accompanies puberty Some of these boys are found to have a low metabolic rate and are seemingly benefited by one to three grains of thyroid daily Whether or not gonadotropin injections should be given before the age of 16 will depend largely on the judgment of the physician Delayed puberty and incipient hypogonadism may be difficult to distinguish at this time If genital growth has not yet started by 16 years there is a good possibility that the boy may turn out to be truly hypogonadal If urinary gonadotropin excretion is not elevated treatment with chorionic gonadotropin should be started as outlined above for hypogonadism

Adiposogenital dystrophy

The uncertainty as to the definition of adiposogenital dystrophy has been noted in Chapter 17 In a prepuberal lad who is fat the penis may be almost completely buried in the pubic fat pad and yet the organ may be actually of average size Even if the penis is truly small no significance can be attached to such a finding in a young boy of 10 to 12 Treatment is therefore directed toward the obesity and consists of caloric restriction If the metabolic rate is distinctly low thyroid may be given If puberal development is delayed the obesity again is managed by dietary control and the gonadal problem is handled as described above Although it is well to rule out a tumor of the hypothalamic region by an adequate neurological examination and x ray studies the vast majority of boys who are diagnosed as adiposogenital dystrophy unlike Froelich s original case do not have such a lesion It has been observed that most of these boys attain normal sexual development by the age of 16 without benefit of any sex hormone therapy [1]

sponse to hormonal stimulation has been reported in bilateral than in unilateral ectopy[7, 12]

The usual regime of hormone therapy consists of 500 I U of chorionic gonadotropin given by injection three times a week If successful this should bring about descent within 1 to 4 months There is no point in continuing beyond 4 to 6 months A mechanically retained gland may be injured by prolonged stimulation in its abnormal habitat If orchiopexy is planned it should then be performed immediately after the unsuccessful trial period because of greater facility in operative manipulation when the testicle has been stimulated with gonadotropin Although surgery is considered to be the final alternative when gonadotropin therapy fails it is pertinent to emphasize not only that mechanical results are poor in about 40 per cent of cases but also that a good functional result is by no means the rule after such intervention Thus of 25 cases of bilateral nondescent reported by Hansen[186] 14 remained sterile after orchiopexy Only two showed perfectly normal semen Moreover Engberg[187] who determined the excretion of androgen in similar groups of patients found that after operation the mean output was identical with that of patients not operated upon i e about half that of the normal adult male Another point of interest is that although malignant tumors are more common in cryptorchid glands (about 1 in 2000 as against 1 in 100 000 for scrotal testes) surgical placement in the scrotum does not necessarily prevent later susceptibility to malignancy In the collected data of Gilbert and Hamilton[14] 77 of the 840 cases of malignancy associated with ectopy were seen in patients previously subjected to orchiopexy

Substitution Therapy

Hypogonadism (eunuchoidism castration)

Substitution therapy is always employed when hypogonadism is due to primary testicular deficiency Since the first use of testosterone esters in hypogonad patients in 1937[5, 18] all who have witnessed the results of androgen therapy testify that the response is little less than dramatic[7, 8*] The various preparations of androgens along with data on dosage for replacement therapy in hypogonadism are described in Chapter 19 For the long continued maintenance which is necessary in hypogonadism the most useful preparations are methyltestosterone given orally or sublingually testosterone cyclopentyl propionate and

See also Chapter 19 references 18–21 24 31 35 39 49 51 52 54–60 63 70 74

There is universal agreement that once pubescence is well under way an undescended testis undergoes tubular degeneration which leads to loss of spermatogenic function Therefore if puberal development is allowed to progress without descent having occurred spontaneously irreparable damage to germinal tissue will ensue There is no unanimity of opinion as to the optimal age when gonadotropin therapy should be employed although no one would advocate surgery before the completion of a trial course of therapy with this hormone Some experienced students of the problem advise such therapy between the ages of 10 and 14 years [5, 8, 11] They choose this age for several reasons There is no histologic evidence of damage to a retained gland at any age before puberty [12, 13] Also if one waits until this age not only will fewer cases of pseudocryptorchism be treated unnecessarily but some truly retained testes will also have descended spontaneously

It may be argued with good logic that if one is to wait until the age of 10 to 14 before instituting therapy it would be just as well to let the normal process of sexual maturation bring about spontaneous descent if such is possible Should such a plan be adopted it is imperative that puberty not be allowed to progress too far If the penis and pubic hair are already well developed and the testis has not begun to descend immediate operative intervention would be recommended by most surgeons One disadvantage of relying on natural puberal processes is the uncertainty of how long to wait A series of injections has the advantage that an answer may be obtained within a short interval of 2 to 3 months while the patient is under a controlled stimulus

There are those who advise gonadotropin therapy between the ages of 7 and 10 [6] and others who advocate treatment even earlier perhaps shortly after birth [9, 10] Proponents of early treatment point out that the natural habitat of the testis is the scrotum at any age and they note that when a testis is brought down in late childhood it is often small and soft and in spite of normal histology may therefore have suffered damage by remaining too long in the aberrant situation

It should be borne in mind that unilateral ectopy never leads to sterility or hormone deficiency as long as the other testis is intact Bilateral cryptorchism persisting into adulthood is almost certain to mean sterility and in occasional instances one observes clinical evidence of hormonal failure There is thus more reason for concern and for early therapy in instances of bilateral involvement It is of interest however that a higher percentage of spontaneous descent or re

There is also no need to start therapy with large doses and later diminish to maintenance levels

In general as the interval lengthens beyond the time that puberty should have occurred the response to androgen is less dramatic After

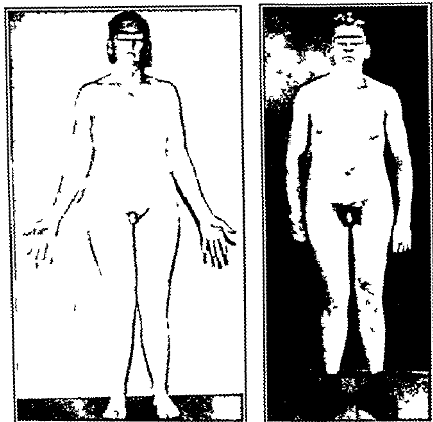


Fig 1 A 37 year old man with hypogonadism (shown also in Fig 5 Chap 17) before and after 3 years treatment with methyl testosterone Growth of the penis and pubic hair owing to the treatment is obvious His weight did not change appreciably but the prominence of subcutaneous fat gave way to a sturdier muscular development

the age of 40 or 50 it may be difficult to stimulate a growth of beard voice change and adequate erectile function

If a successful course of therapy is ultimately interrupted many of the anatomic acquisitions do not regress Just as after postpuberal castration the masculine voice persists there is only slight decrease in penile dimension and facial hair diminishes if at all only very slowly

testosterone pellets The choice depends largely on the preference shown by the patient

Effects appear promptly although some anatomic changes are slower in developing than others Spontaneous erections in great number are often noted within 24 hours An increased frequency of erection is almost certain to appear before the end of the first week On large doses this stimulation may approach actual priapism After several days of therapy hyperemia of the penis and scrotum is sometimes noted Within 2 to 6 weeks there is enlargement and darkening of the scrotum and penis enlargement of the prostate and the appearance of ejaculate In complete hypogonadism the testes do not enlarge and spermatozoa do not appear although the epididymis and adjacent structures may become more prominent After 1 to 4 months pubic hair becomes thicker and the voice begins to deepen A small mass of tender breast tissue similar to that commonly seen at puberty may appear beneath the nipples within several months and acne often develops at about this time After 2 to 6 months axillary hair increases and facial and body hair may begin to grow Complete development of the beard may be delayed for one or more years The excessive number of erections breast enlargement and acne tend to diminish as therapy is continued over a period of months or years

In addition to specific masculinizing effects there are other important systemic responses Increased appetite with weight gain is to be expected The increment in weight is due in large measure to increased muscle mass Body contour thereby becomes more masculine (Fig 1) Hot flashes if present cease Sex desire tends to increase emotional balance improves and there is increased energy and sense of well being The psychological changes are probably in no small part due to the patient s realization that his physical and sexual defects are in process of repair

Other changes to be expected are increased tanning and ruddiness of the skin a slight rise in red blood cell count and hemoglobin and some degree of increase in basal metabolic rate If the epiphyses are not fused a spurt in growth and an accelerated closure of the epiphyseal centers is commonly encountered Testosterone (VIII) and its esters tend to inhibit creatine excretion whereas methyltestosterone (XCVI) increases the output of this compound

Except for a decline in excessive number of erections subsidence of breast stimulation and improvement of acne a real tolerance to exogenous androgen does not develop after indefinitely prolonged therapy There is no reason for an ultimate increase in dosage unless initial doses had been kept small to prevent excessively frequent erections

height any greater than would in time be spontaneously attained Unfortunately there are no pituitary extracts sufficiently potent and pure

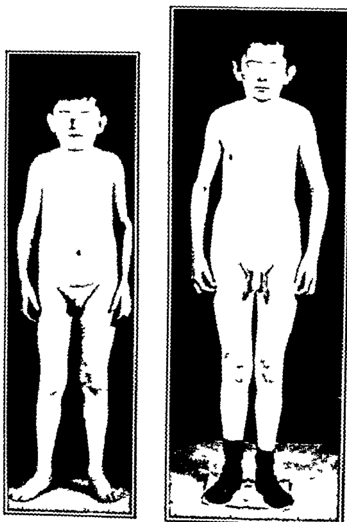


Fig 2 Pituitary dwarfism at age 17 and again after 4 years of irregular treatment with testosterone pellets and methyl testosterone In addition to growth of the penis scrotum and a small amount of pubic hair his height increased from 51 inches to 57 and bone age advanced from 7 years to 15 years

or persistently effective after prolonged administration to stimulate growth in the human being

For girls with pituitary dwarfism estrogen therapy promotes growth of the breasts and the secondary genital apparatus but in order to

over a period of years On the other hand the prostate gland regresses very promptly and ejaculate decreases or disappears Erections decrease in frequency sex interest tends to decline and body weight is lost Physical vigor and emotional stability may again be impaired

The male climacteric although not usually termed hypogonadism represents a state of androgen deficiency which requires replacement dosage of the same general magnitude as in eunuchoidism Since oral methyltestosterone (XCVI) is reported in some cases to have a lesser effect than injected testosterone propionate (LXXXIX) (Chapter 19) it is advisable to use the latter for a therapeutic test If success is evident methyltestosterone (XCVI) may then be tried or pellets of testosterone (VIII) may be implanted

Androgens in Miscellaneous Disorders

There are many hundreds of reports in the literature which are concerned with the use of androgens in a variety of clinical disorders not due to gonadal disease Since most of these disorders are not immediately fatal we not only lack a definitive end point by which the alleged therapeutic benefit may be judged but we also are deprived of the motivation to save life which often inspires and finances large scale well controlled projects in clinical research The point being made is that because of the paucity of data the conclusions which are recorded in the remaining sections of this chapter are sometimes colored in no small degree by *impressions* and *opinions*—both of others in the field and of the present writers

Pituitary dwarfism Simmonds' disease (panhypopituitarism)

Pituitary deficiency in childhood is characteristically accompanied by dwarfing and hypogonadism Unless there is complete destruction by a tumor a serious loss of all the hormonal secretions of the gland is not the rule For example frank adrenal insufficiency is uncommon and hypothyroid features are variable In the male after the age of normal puberty is passed the hypogonadism is perhaps the most serious defect which the patient endures Fortunately by androgen administration it is possible to bring about normal masculinization [1, 3] The dosage is similar to that required for eunuchoidism By virtue of a stimulation of bone growth these boys will undergo a considerable spurt in stature while under therapy[177] (Fig 2) However in that epiphyseal closure may thereby be accelerated [5, 54, 65, 81] it is doubtful whether this increment in growth will lead to an ultimate

As to a relative estrogen excess it should be noted that although hyperplasia and metaplasia of certain epithelial areas of the prostate may be induced by estrogen the nodular growth typical of benign hypertrophy is not reproduced If urinary androgen estrogen ratios were obtained on patients with benign hypertrophy a more rational basis for the appraisal of the foregoing theories would be available

The relative estrogen excess theory *although unsupported by fact* has been largely responsible for the widespread trial of androgen therapy in this disorder After more than 10 years of clinical use both in this country and abroad the following statements seem reasonable (1) Androgen therapy causes no perceptible change in the gross size or histological structure of the gland It is therefore useless when urinary obstruction is severe (2) Some patients (perhaps one third to one half) claim to be improved as far as symptoms are concerned They testify to having less difficulty in initiating the flow of urine greater force of flow and decreased frequency Actual measurements of residual urine usually reveal little or no real decrease

Some of the earlier references to the literature on androgen therapy are given by Heckel[1, 2] Among the various authors who have reported on this treatment optimism varies inversely with the rigorousness of the analysis of results Draper and workers[113] for example used control injections of saline in part of their cases and found about 50 per cent improvement with either saline or testosterone propionate (LXXXIX) (25 mg daily) These authors also point out that many patients with mild prostatism have been observed to improve symptomatically as time goes on without any treatment Thus a favorable response to treatment may be due in part to simple suggestion or to coincidence

It is only fair to point out that there is some evidence which supports the idea that bladder muscle stimulation may follow the injection of male hormone[33] Expulsion of urine might thereby be facilitated in spite of an abnormal urethral resistance

As to the anatomic status of the gland in prostatism it can logically be reasoned that whereas androgen deprivation leads to atrophy of the normal prostate castration might likewise cause shrinkage in the presence of pathologic hypertrophy As a matter of fact castration was practiced for this purpose as early as 1893 and recent histologic studies verify that the epithelium of the hypertrophic tissue does actually shrink after orchectomy[3] Gross shrinkage of the entire mass of hyperplastic tissue is however variable in degree and incomplete The absence of any invariable or dramatic change may be due to the site of origin of prostatic hyperplasia in man which is often if not

attain complete growth of sexual hair and maximum growth in stature androgen should also be given [23, 24]. The dosage which has been employed in conjunction with 1 mg of diethylstilbestrol (CCXVI) is 10 to 25 mg methyltestosterone (XCVI) orally daily. Too large a dose may lead to undesirable masculinization.

In the adult damaging lesions of the pituitary are often attended by complete destruction of the gland and hence in addition to gonadal failure there are usually serious deficiencies in thyroid and adrenal function (Simmonds disease panhypopituitarism). The administration of thyroid and adrenal hormones alone usually does not effect a satisfactory recovery of strength or a marked gain in weight. Androgen in the usual replacement dosage with or without simultaneous use of the other two hormones brings about nitrogen storage, gain in weight, increased strength, hemoglobin regeneration, and in general a much closer approximation to a normal healthy state [25, 8]. The hormone also restores secondary sex characteristics in the male and promotes sexual hair growth in the female.

Benign prostatic hypertrophy

The cause of prostatic hypertrophy is unknown. An endocrine etiology has long been suspected but never satisfactorily proved. The diversity in theories of endocrine causation is illustrated in the following tabulation:

Proponent of Theory	Physiological Initial Disturbance	Secondary Change	End Result
Lower [29]	Failure of production of a pituitary suppressing hormone (Inhibin) by testicular tubules	Increased stimulation of Leydig cells by pituitary and thus enhanced androgen secretion	Prostatic hypertrophy from absolute androgen excess
Wugmeister [30]	Estrogen deficiency	Relative excess of circulating androgen	Hypertrophy from relative androgen excess
Van Cappellen [31]	Failure of testicular androgen production	Relative excess of circulating estrogen	Hypertrophy from relative estrogen excess

It is not difficult to raise objections to any one of these three theories. For example, although there is evidence that the testicular tubules may elaborate a hormone which depresses the pituitary gland, there is certainly no indication that excess androgen is produced late in life.

abnormalities during a standard exercise test. Husemann does not report such effects from the hormone. The influence of emotion on angina is well known, and the conservative observer would prefer to interpret beneficial effects, when they occur, as due to an improved emotional status which has been promoted either by the needle or by relief of a concomitant climacteric state.

Peripheral arteriosclerosis was found to be uninfluenced either functionally or anatomically in a controlled study of cases adequately treated with male hormone.[9] Steinach and co-workers claimed that *hypertension* was usually reduced by androgen therapy.[3, 4] Subsequent studies have failed to confirm this observation,[3, 5, 8] and one may expect no significant clinical effects of androgen on blood pressure when given in ordinary therapeutic doses.

Promotion of anabolism in various disorders

The well-known anabolic function of the androgens is manifested in their capacity to promote synthesis of protein not only in muscle but also probably in most tissues of the body.[2, 163] This property has led to the use of male hormone in a variety of clinical conditions not attended primarily by androgen deficiency. In such instances it is often undesirable to stimulate the development of secondary male sex characteristics. Attempts to discover steroid compounds with little or no masculinizing properties but with well-marked anabolic activity have, however, not met with unequivocal success. Although methyl androstenediol (CXXXIII) has achieved a certain notoriety in this regard, data which would indicate a peculiarly high ratio of anabolic to androgenic potency are little more than suggestive.[150, 182] That its androgenic potency is weak in man, as in animals, is indicated by a low incidence of virilization in women receiving rather large doses.[83] In man, although anabolic activity has been demonstrated, therapeutic results have not been striking when the compound has been administered for the specific purpose of promoting anabolism.[3] It would be premature to recommend this compound as a nonvirilizing anabolic steroid until extensive quantitative studies at various levels of dosage have demonstrated a unique superiority over the common androgens. Preliminary animal experiments with 19-nortestosterone (CLXXI) suggest that this compound shows some promise (Chapter 8).

CUSHING'S SYNDROME. Albright in 1941[4] proposed that Cushing's syndrome, being undoubtedly a form of adrenal cortical hyperfunction, was in essence a manifestation of protein depletion which involved muscles, skin, blood vessels and the matrix of bone. The protein wastage could be ascribed to excessive production of the com-

always in the submucosal glands of the prostatic urethra The prostatic urethra *at least in the rat show no atrophy after castration*[35] Although some patients are relieved of symptoms by orchectomy the certainty of any material success is not great enough to warrant such radical therapy The operation fell into disfavor at the turn of the past century

Estrogen which in effect produces functional castration by its inhibitory action on the pituitary may cause some shrinkage of the *enlarged gland and give symptomatic relief in some cases*[0, 36, 118] However clinical improvement is not striking

It is apparent that dramatic cures of prostatism are not to be expected from the administration or deprivation of sex hormones Surgical resection still remains the most effective method of treatment

Cardiovascular disease

There have been a number of reports claiming a favorable effect of androgen in angina pectoris With 25 mg of testosterone propionate (LXXXIX) given one to three times weekly a decrease in the severity and the number of attacks has been reported in 25 per cent[37] to 90 per cent[38] of cases The reason for apparent improvement in some cases is not known however and enthusiasm for this therapy is completely wanting among many who have tried it The spontaneous waxing and waning of symptoms often encountered in this disorder makes satisfactory evaluation of therapy difficult It should also be remembered that all precordial and substernal pain is not true angina

Angina pectoris is due to coronary sclerosis There is no indication whatever that androgen deficiency predisposes to coronary disease On the contrary the predilection of the disease for males suggests that androgen could conceivably be a positive factor in its pathogenesis If symptoms are truly relieved by testosterone one might seek the reason among the following mechanisms (1) dilatation of coronary vessels (2) alteration of the myocardial metabolism so as to enable the heart to better tolerate a relative ischemia (3) promotion of growth of collateral blood channels and (4) improvement of the emotional status of the patient either by the relief of an incidental androgen deficiency which by chance would be present in some patients at this age or by the nonspecific placebo effect that *any* therapy might provide

Although it has been reported that arterial blood flow of the skin is enhanced by androgen[39] there is no direct evidence of such an effect on the coronary system neither is there any convincing support for mechanisms 2 and 3 above And although Waldman[40] reported improved physical *tolerance along with slight diminution in cardiographic*

OSTEOPOROSIS OF LATE LIFE Women after the menopause are more susceptible to a serious degree of osteoporosis than are elderly men Dramatic relief of pain from the spine lesion has frequently been observed during estrogen therapy and a detectable increase in calcification has been noted in some cases after prolonged therapy [93] If as Albright believes the dissolution of bone matrix which characterizes osteoporosis is attributable to a low level of sex hormone one would hope for an even better repair of the osseous defect by the action of androgen Estrogen is actually a rather weak anabolic hormone Clinical experience with these patients is as yet limited nevertheless calcium balance is reported to be more strongly positive with combined estrogen and androgen administration than with either hormone alone [103] A typical regime would consist of 1 mg diethylstilbestrol (CCXVI) and 20 mg methyltestosterone (XCVI) given daily The relative and absolute amounts of estrogen and androgen can be varied with the sex of the patient and with the susceptibility of the individual to virilization or feminization as the case may be Excellent symptomatic relief has been obtained with testosterone propionate (LXXXIX) alone in doses of 25 mg one to three times weekly [1]

INDUCTION OF POSITIVE NITROGEN BALANCE IN MISCELLANEOUS DISORDERS The massive albuminuria of nephrosis drains heavily on the protein stores of the body Testosterone propionate (LXXXIX) 25 to 50 mg daily promotes protein storage in this disorder However in the one reported case there was no marked rise in plasma protein level and an accentuation of edema due presumably to the sodium retaining effect of the hormone was an undesirable side action [8] There are indications that in some circumstances androgen may actually depress the quantity of plasma protein in circulation perhaps because of its increased conversion to tissue protein

Although Butler and co workers [59] were able to achieve a slight conservation of nitrogen by giving androgen to subjects ingesting a protein free diet they were uncertain whether the over all effect was beneficial

The stress of trauma or infection leads to an initial catabolic reaction characterized by a negative nitrogen balance There is as yet no decision as to whether it is advantageous to oppose this reaction routinely by vigorous therapy of any kind Testosterone propionate (LXXXIX) has been tried for this purpose after thermal burns [58] The same preparation in doses of 25 to 50 mg per day has been shown to enhance nitrogen retention in patients convalescing from severe trauma and receiving an adequate diet [104] The daily administration of 50 to 100 mg to paraplegic patients has been reported to improve the ni

mon adrenal corticoids such as hydrocortisone (CXV) and cortisone (CXVI) which have a catabolic or anti anabolic function and which therefore favor degradation of body tissues by conversion of protein to amino acids and glucose Hence androgen was given to several patients with Cushing's syndrome [testosterone propionate (LXXXIX) 25 to 50 mg or methyltestosterone (XCVI) 25 to 100 *mg* daily] Retention of nitrogen potassium and calcium was demonstrated along with a gain in strength and improvement of the bone and skin disorders

Others have subsequently confirmed these metabolic results although the clinical improvement has not always been so striking If the cause of the syndrome in a given case is an operable adrenal tumor the recommended treatment is of course its surgical removal It is in cases *presumably due to functional overactivity of the adrenal* cortex wherein androgen therapy may be beneficial The hormone probably not only antagonizes the excess of circulating adrenal hormone but also suppresses its formation by inhibition of ACTH secretion [46] Doses required which are at the virilizing level for women may be expected to accentuate the existing hirsutism and will not restore the menses In general androgen administration cannot be considered a specific or practical form of therapy Results with bilateral adrenalectomy are considerably *more satisfactory* in cases due to functional hyperadrenalism

Addison's disease In addition to the deficiency of corticoids which affect electrolyte and carbohydrate metabolism a destructive lesion of the adrenal cortex in the female also leads to a loss of the only important source of androgen in this sex If androgen has any significant anabolic function in the female one would consider using the hormone in women as an adjuvant to the usual therapy in Addison's disease The usual nitrogen retaining effect of androgen has been demonstrated in the Addisonian patient [48] There is however relatively little evidence in the literature bearing on the clinical efficacy of such complementary treatment Williams and workers report only slight to moderate improvement in strength and energy [9] In our own experience to date no dramatic effects have been noted Nevertheless when weight appetite and strength are not adequately restored by maintenance therapy with desoxycorticosterone (CXXI) and/or cortisone (CXVI) it is well to try androgen at the usual substitution dose level along with the basic cortical hormone treatment Sodium retention although promoted by androgen [9] is so easily accomplished by desoxycorticosterone (CXXI) that a supplement of any other hormone for this purpose would be superfluous

2 to 3 weeks fairly well rules out androgen deficiency as the cause of the disorder. A positive response to such therapy of course does not establish the diagnosis unless one excludes the effect of suggestion by a similar trial with blank injections.

Psychoses of middle and late life

The frequent occurrence of melancholia and related disorders at the menopause or late in life might suggest that sex hormone deprivation is a common cause of such psychoses. There is certainly ample evidence that even gonadectomy in either sex does not usually lead to a psychosis. However the possibility still remains that the stress incident to hormone withdrawal during the climacteric might in occasional cases contribute to the precipitation of a psychotic state provided that the person is vulnerable to mental illness.

Clinical results with androgen therapy in involutional melancholia in either the male or female indicate that a small number of patients improve. Case reports and references to the literature may be found in papers by Rothermich[66] Danziger[73] and Altschule[99]. About one fifth of the total number of patients treated have shown marked improvement or recovery after 3 to 4 months of treatment with testosterone propionate (LXXXIX). This percentage is not as favorable as that obtained with shock therapy and indeed is not as high as the expected *incidence of ultimate spontaneous recovery*. However Danziger points out that it is substantially higher than would be expected in a comparable time interval if all treatment were withheld. Rothermich and workers found that favorable results were encountered more frequently in atypical depressive states than in cases of classical involutional melancholia with a characteristic prepsychotic personality. The dosage usually employed is 25 mg testosterone propionate (LXXXIX) two to three times a week. Altschule gave 50 mg of the hormone daily in order to obtain an effect beyond that of simple replacement therapy. The purpose of the large dosage was to produce a metabolic stress reaction similar to that which has been observed after electro shock treatment.

According to present evidence androgen therapy does not provide the specific and relatively predictable curative effect which is obtainable with electro shock treatment. It may be tried in male involutional melancholia or given as an adjunct to shock treatment if male hormone deficiency is believed to contribute to the over all clinical picture. If the patient is a female there appears to be no proved advantage of androgen over estrogen.

trogen balance and decrease the incidence of decubitus ulcers[169] Preoperative and postoperative therapy of patients who were poor surgical risks was attended by an improved nitrogen balance and the prevention of postsurgical liver dysfunction[195]

In a limited series of cases with persistent liver involvement after viral hepatitis androgen was shown to reverse the negative nitrogen balance and apparently promote some degree of clinical improvement[170] Twelve men with severe cirrhosis are reported to have acquired better strength appetite emotional stability and sex function after androgen was added to the routine dietary program[171]

It has been reported that methyltestosterone (XCVI) 5 0 mg daily given with feedings or dropped on the tongue in propylene glycol solution immediately after birth promoted more rapid weight gain in a group of premature infants over a 3 week period than in a group of untreated controls[60] Mortality rate was not affected Hardy and Wilkins[17] were unable to demonstrate such an affect in their series of infants where therapy was initiated at the age of 7 to 10 days

Impotence and low sex drive

Hamilton's observation that androgen has a specific capacity to stimulate penile erection[61] gave hope that this hormone might be useful in the treatment of impotence Unfortunately it soon became clear that this capacity of androgen was manifested only in the presence of a pre existing deficiency of testicular secretion (prepuberal boys eunuchs eunuchoids and occasional cases of the male climacteric) Both sex drive and erectile function in man are sustained by a combination of humoral and psychic forces Failure of either component may lead to a loss of sex interest or impaired ability of erection However when patients with these complaints are critically studied only a small minority are found to be suffering from androgen deficiency This holds true particularly in the younger age group Administration of androgen to normal men does not stimulate the sex drive Likewise if low sex interest or impotence are due to emotional or nonendocrine factors an additional increment of androgen supplied by the exogenous route is of no avail[6 -65]

Admittedly the diagnosis of an acquired androgen deficiency is not easy in an adult male whose sex apparatus appears physically normal (Chapter 17) Emotional factors likewise are often difficult to uncover and to evaluate A course of trial therapy with androgen is perhaps the best procedure in questionable cases[6] Failure to respond to 25 mg testosterone propionate (LXXXIX) three times a week for

to an alleviation of the hypogonadal component rather than to a direct effect on the muscular dystrophy One out of a small series of boys with progressive muscular dystrophy seemed to improve on 20 mg daily of testosterone propionate (LXXXIX)[82] One adult woman whom we have seen has shown slight improvement in strength and substantial weight gain on 25 mg two to three times weekly[83]

Certain cases of myasthenia gravis appear to be somewhat relieved by *methyltestosterone* (XCVI) 20 to 50 mg daily[83 84]

Androgen has no proved curative effect in any of the muscular dystrophies and the modest improvement which is occasionally seen probably results from a nonspecific anabolic effect of the hormone on the muscular system

Kidney damage

The use of androgen in lipoid nephrosis has been discussed previously under the section on anabolic activity (page 345)

Androgens have a renotropic action which is manifested in experimental animals by hypertrophy of the tubular epithelium Partial protection against the lethal effect of mercuric chloride has been reported in rats (Chapter 13) The usefulness of the hormone in clinical cases of reversible tubular necrosis (caused by bichloride CCl_4 sulfa drugs) for the purpose of accelerating tubular regeneration is thereby suggested However there are no available statistics on adequate clinical trials The dose of testosterone propionate (LXXXIX) in man calculated on the basis of the rat experiments would be in the range of 0 5 to 1 0 gram daily

There is a report of clinical benefit and substantial reduction in mortality with 25 mg of testosterone propionate given daily to patients suffering from Asiatic chlorea complicated by the presence of uremia[85] It is difficult to evaluate the reported results The mortality statistics in cholera vary over wide limits largely because of variations in completeness of the simple supportive treatment which is of prime importance in the therapeutic regime When uremia occurs the mortality is said to be particularly high It is not easy however to define what is meant by uremia because nearly all cholera patients suffer some degree of oliguria proteinuria and azotemia due to the extreme electrolyte depletion and dehydration which accompany the disease

Sterility

Androgen when given to normal male rats may either stimulate or depress spermatogenesis (Chapter 11) The type of effect varies with

Homosexuality

The relation of sex hormones to sexual behavior has been discussed in Chapter 12. In normal animals sex hormones tend to intensify existing sexual behavior patterns rather than to reverse them. Several reports are available on the treatment of homosexuality with androgen.[74-77] In well documented cases of overt, well defined homosexuality there have been no instances of striking reversal to a heterosexual type of interest or outlet. A few apparently successful results have been claimed when the condition was latent, or where it was encountered to a rather minor degree in boys whose puberal development was retarded. A certain amount of homosexual activity is not rare during normal adolescence, however, and such behavior often tends to decline spontaneously as maturity advances. Establishment of heterosexual interest at this age by androgen therapy probably consists merely of an artificial acceleration of normal psychosexual development. Hormone therapy is justified if a distinctly delayed puberal development is the source of psychological complications and poor heterosexual adjustment. (See page 332.)

Simple gynecomastia

Complete or partial regression of simple breast enlargement in mature men was reported by Hoffman in 1939 in a series of nine patients treated with testosterone propionate (LXXXIX).[78] There have been no subsequent reports of such a consistently good response. Dunn,[79] for example, observed no improvement in three cases and no recession has been noted in Klinefelter's syndrome during androgen therapy.[80] It is possible that some of the purported responses may represent spontaneous remissions, which are frequently encountered in this disorder.

There is no justification for routine treatment of gynecomastia with androgen. The chronic postpuberal type is best handled by surgical excision of the hyperplastic tissue. The slight breast enlargement seen frequently at puberty is probably indeed due to stimulation by endogenous androgen and administration of additional hormone would be irrational. In any event, the condition is a transient and benign process in the great majority of boys.

Muscular dystrophies

Increased strength was noted in myotonia atrophica (dystrophica myotonia) after administration of androgen but only when there was an associated testicular atrophy.[81] The effect was therefore attributed

to an alleviation of the hypogonadal component rather than to a direct effect on the muscular dystrophy One out of a small series of boys with progressive muscular dystrophy seemed to improve on 20 mg daily of testosterone propionate (LXXXIX)[82] One adult woman whom we have seen has shown slight improvement in strength and substantial weight gain on 25 mg two to three times weekly[83]

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Sterility

Androgen when given to normal male rats may either stimulate or depress spermatogenesis (Chapter 11) The type of effect varies with

the dose and the age of the animal If administered immediately after hypophysectomy the hormone will prevent tubular atrophy and will maintain spermatogenesis The evidence is therefore valid that at least in this animal androgen plays a part in the sustenance of the testicular tubules In the normal human male as will be noted at the end of this chapter ordinary therapeutic doses actually depress the sperm count It is probable that although a normal amount of circulating androgen is beneficial and certainly not harmful to the tubular epithelium the excess amount which accrues from injected hormone added to the normal endogenous supply may suppress the secretion of pituitary gonadotropic hormone (FSH) which normally serves to support tubular integrity

If occasional cases of sperm inadequacy exist which are due to an inadequate supply of androgen it would be anticipated that male hormone would be beneficial One would expect this type of case to be characterized clinically by the usual eunuchoid features which are associated with androgen deficiency There have in fact been several cases of hypogonadotropic eunuchoidism reported in which androgen therapy has been attended by the appearance of sperm in the ejaculate [6] [165] [184] In some of these patients spermatogenesis was known to have been absent before therapy Whether in these cases the androgen exerts a direct effect on tubular maturation or simply acts as a trigger to initiate pituitary activity cannot be said with certainty The failure of the low urinary gonadotropin to rise in some of these cases is suggestive of a direct tubular effect In other instances [165] where spermatogenesis has persisted after therapy has been withdrawn a trigger mechanism is suggested There are several cases on record in which low sperm counts were seen to rise during therapy in individuals who were not described as frankly eunuchoid [11] [114] Such an effect however has not been commonly observed

Heller [173] Heckel [1] and co workers have demonstrated a remarkable rebound of spermatogenesis when androgen was given to men who showed oligospermia but whose endocrine status had appeared normal During the period while testosterone propionate (LXXXIX) was being given in doses of approximately 50 mg three times a week for 1 to 3 months the sperm count was further reduced to levels of azoospermia and biopsies revealed a more severe derangement of germinal elements than before There was tubular necrosis with hyalinization and disappearance of Leydig cells Gonadotropin excretion declined Within 5 to 6 months after discontinuance of androgen the sperm counts rebounded far above pretreatment levels in approximately half the cases whereas testicular biopsies showed not only re

covery from the depression which attended androgen administration but also an appearance often much improved over that of the control specimens. The improvement was still apparent two years later in some instances but in others recession occurred several months after the peak of the rebound.

Skin disorders

Although androgen has been used in a few cases for the treatment of acne and some of the patients were said to improve there is no reason to believe that the hormone was responsible. On the contrary there is good evidence that male hormone is an important factor in the causation of acne.[90]

Good results have been reported in *senile pruritus* in men who have received testosterone propionate (LXXXIX) in doses ranging from 5 to 25 mg once a week or testosterone (VIII) ointment (4 mg daily).[91, 92] The pruritus of jaundice is said to be relieved by methyl testosterone (XCVI) (25 mg daily sublingually).[5]

Postmenopausal *pruritus vulvae* is said to respond favorably to the local application of testosterone (VIII) ointment.[94]

Hyperthyroidism

Male hormone was used in the treatment of hyperthyroidism as early as 1938[95] but the number of cases treated so far has been small. The dose employed has ranged from 25 mg testosterone propionate (LXXXIX) three times a week to 50 mg daily in both male and female patients. Reports indicate that although one may commonly expect subjective improvement and weight gain more often than not there is no appreciable fall in the basal metabolic rate.[96–98]

The clinical improvement which has been noted is most likely attributable to the over all anabolic action of the hormone rather than to any direct influence on the thyroid or pituitary glands. Nitrogen and calcium are retained and creatinuria is decreased.[97] Methyltestosterone (XCVI) leads to an ill sustained retention of nitrogen but increases the creatinuria and apparently aggravates the subjective symptoms of the disease.

Testosterone (VIII) is not to be advocated as a sole therapeutic agent in thyrotoxicosis. It may be of aid as an adjunct in selected patients who as a result of the disease have suffered a serious weight decline and substantial loss of muscle mass.

the dose and the age of the animal If administered immediately after hypophysectomy the hormone will prevent tubular atrophy and will maintain spermatogenesis The evidence is therefore valid that at least in this animal androgen plays a part in the sustenance of the testicular tubules In the normal human male as will be noted at the end of this chapter ordinary therapeutic doses actually depress the sperm count It is probable that although a normal amount of circulating androgen is beneficial and certainly not harmful to the tubular epithelium the excess amount which accrues from injected hormone added to the normal endogenous supply may suppress the secretion of pituitary gonadotropic hormone (FSH) which normally serves to support tubular integrity

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Heller[173] Heckel[1 4] and co workers have demonstrated a remarkable rebound of spermatogenesis when androgen was given to men who showed oligospermia but whose endocrine status had appeared normal During the period while testosterone propionate (LXXXIX) was being given in doses of approximately 50 mg three times a week for 1 to 3 months the sperm count was further reduced to levels of azoospermia and biopsies revealed a more severe derangement of germinal elements than before There was tubular necrosis with hyalinization and disappearance of Leydig cells Gonadotropin excretion declined Within 5 to 6 months after discontinuance of androgen the sperm counts rebounded far above pretreatment levels in approximately half the cases whereas testicular biopsies showed not only re

of normal testes A damaging effect has been repeatedly observed in various species of immature animals after the injection of physiological amounts of testosterone propionate (LXXXIV) (Chapter 11) To be sure there is evidence in the rat that this damage is reversible if injections are terminated before puberal development is under way Both the spermatogenic and endocrine functions of the gland have been reported to return to normal in the adult animal[108] One would feel more secure however if such were also known to hold true for man

A less serious deterrent to the use of androgen during childhood is precocious masculinization with its attendant undesirable psychological implications in certain children The degree of masculinization need not be extreme however if courses of therapy are short and the dose of hormone is kept as low as possible

BODY STATURE Androgen as an anabolic stimulant will not only augment muscle mass but also will promote growth in stature provided that the epiphyseal centers are still open In the treatment of prepuberal boys for various disorders both chorionic gonadotropin and testosterone compounds have been repeatedly noted to cause a spurt in growth[43, 1, 51, 104, 105] The usefulness of androgen in pituitary dwarfism has already been pointed out Ought this hormone be used to enhance stature in boys whose growth is stunted for other reasons? If the cause is a nutritional one treatment should be directed toward relief of the underlying disorder or correction of the faulty diet Some stunted boys who represent nutritional problems but who are not relieved by dietary adjustment are reported to respond well to short courses of androgen therapy (20 mg methyltestosterone (XCVI) daily for 3 to 6 months)[0] Androgen if used at all should however be given only after simpler corrective measures have failed The question of whether ultimate adult height will be greater as a result of a spurt induced by androgen can be raised for these children just as it has been for pituitary dwarfs It has been suggested however that the probable depression of the pituitary gland attendant on malnutrition might be alleviated by the impact of a short course of such therapy[105] If this were the case the attendant growth would be less artificial

It is worth noting at this point that on theoretical grounds and on the basis of animal experiments androgen could logically be tried in an attempt to retard growth. If large doses were given over a long period of time during the prepuberal years some degree of suppression of hypophyseal growth hormone might result and moreover the sexual precocity so induced would be accompanied by premature epiphyseal closure Such therapeutic efforts should of course be reserved for

Lupus erythematosis

Preliminary trials suggest that androgen may be of value in the treatment of the discoid variety of lupus Doses of 10 to 40 mg of methyl testosterone (XCVI) per day by the buccal route have been followed by remissions in the majority of patients in a small series of cases[187 188]

Simple senility

The well marked decline in the excretion of 17 ketosteroids and androgens which accompanies advancing age most certainly reflects a decrease in the internal secretion of androgens Whether such a hormonal decline can be blamed as a cause or even as a contributing factor in the development of any of the physical and mental infirmities of old age (with the possible exception of osteoporosis) is certainly not established The probable rarity of a true climacteric state in older men has been noted in Chapter 17

The administration of androgen may stimulate sexual activity in senile rats (Chapter 12) but physical rejuvenation has not been reported When 25 mg doses of testosterone propionate (LXXXIX) were given daily for a week to two 76 year old men the expected anabolic response as evidenced by nitrogen retention was noted[100] Although no clinical changes were observed the duration of treatment was suboptimal for such an evaluation That certain end organs of senile men may respond to additional androgen is indicated by acceleration in growth of facial hair during testosterone administration[1 6] An early report from France indicated that testosterone propionate (LXXXIX) given in daily doses of 20 to 40 mg for 2 weeks to six senile men promoted a weight gain of about 5 pounds and there was also some evidence of improvement in muscular strength in resistance to fatigue and in psychomotor performance[101] There is also a report that methyltestosterone (XCVI) in daily doses of 20 to 40 mg increased the fusion frequency of flicker the strength of back muscles and the work performance in a small group of older men who complained of fatigue[164] Placebo controls were used in this study On the other hand a more recent well controlled study of a large group of senile men showed no improvement in muscular or psychomotor performance while the subjects were receiving 75 mg of methyltestosterone (XCVI) daily over a one month period[10]

Miscellaneous disorders of childhood

There is a feeling on the part of conservative endocrinologists that androgen should be given with caution to any child who is possessed

the patient under treatment The physiological alterations of the female reproductive system which accompany the administration of androgen have been discussed in Chapter 11 The discussion here will be confined to the clinical usefulness of the hormone in a number of disorders The reader is referred to the article by Carter Cohen and Shorr[116] for a comprehensive review of androgen therapy in the female

MASCULINIZING EFFECTS OF ANDROGEN At the outset it should be emphasized that androgen when given to a woman in sufficient *dosage* and for a sufficient *length of time* can always be made to cause some degree of what can broadly be called masculinization In some disorders however either the dose requirement may be low enough or the duration of treatment sufficiently short that this complication is avoided In other instances where large sustained doses of hormone are necessary the possible benefit derived may compensate for the undesirable side effects

The virilizing phenomena vary from one patient to another in form and degree but there is a familiar pattern which is fairly constant Organs which are involved include the hair (hirsutism) skin (acne) clitoris (enlargement) and larynx (voice change) The predominance of the effect on one tissue as compared to that on another varies with the susceptibility of the separate end organs Increased facial hair growth an early manifestation is usually first detectable as a lengthening and thickening of the hair on the upper lip followed by its appearance on the cheeks and chin The stimulation of generalized body hair growth or induction of baldness requires rather large and prolonged dosage Brunettes are said to be more susceptible than blond women however this impression may be related to the greater visibility of darkly pigmented hair After treatment is stopped the excess hair tends to diminish but complete reversal may not be achieved in less than 6 or more months

Acne may range in severity from increased oiliness and comedo formation to a frank pustular eruption It may decrease as treatment is extended and it also subsides rapidly upon withdrawal of the hormone Another skin reaction sometimes encountered is a red flush most marked on the face

Frank clitoral enlargement usually requires higher doses than the minimal level which will alter the hair or skin although hyperemia and increased sensitivity are rather easily induced with moderate doses In the presence of marked hypertrophy regression after cessation of therapy may require many months

those rare cases of true pituitary giantism in which the seriousness of the disorder justifies such radical interference with sex hormone physiology

UNDESCENDED TESTES The treatment of undescended testes with chorionic gonadotropin is discussed at some length in the section on stimulation therapy Although testosterone will bring about descent in a certain number of cases the percentage of success is lower than with chorionic gonadotropin [107] The latter is the preferred therapeutic agent

SMALL GENITALIA Also discussed elsewhere under stimulation therapy is the inadvisability of treating a prepuberal boy with hormone simply because his genitals are of below average dimensions Penile growth may of course be achieved very simply by the use of methyl testosterone (XCVI) orally [108] The question which is raised is not that of efficacy but rather of the necessity or advisability of such therapy

ENURESIS Because of the belief that many cases of enuresis in children are secondary to an immature state of the urogenital structures methyltestosterone (XCVI) has been given to both boys and girls in daily doses of 10 to 20 mg for 1 to 3 months [109, 110] Complete cures are recorded in 20 to 50 per cent of cases and failures in 2 to 16 per cent The usual fluid restriction and psychological precautions were observed at the same time although for many of the patients these measures had previously proved ineffectual In a disorder where emotional factors are so important the appraisal of any therapy is difficult One would commend the use of simultaneous controls in clinical trials of this sort

Androgen therapy in enuresis has not attained general acceptance It is very likely that submasculinizing doses are ineffective Masculinizing doses although conceivably effective in some instances are to be condemned in the young child with a functional disorder of this nature

SEPARATION OF PREPUCE Testosterone propionate (LXXXIX) has been used successfully by local application to facilitate separation of an adherent foreskin in infants [111]

Disorders of the female reproductive system

Although no discrete entities due to androgen deficiency have been identified in woman nevertheless androgens being secreted normally by the adrenal cortex are not foreign to this sex and therapy with a compound such as testosterone is artificial only in the sense that circulating androgen is raised to a level above that usually present in

even before the more obvious use of the hormone in eunuchoidism was reported During the succeeding years extensive clinical trials in menopausal patients have consistently borne out the early observations and there is no doubt that the familiar vasomotor symptoms along with most of the other characteristic *complaints usually* respond quite favorably to this hormone provided that the dose is large enough The mechanism of action is no better understood than is that of estrogen Androgen like estrogen will reduce the elevated gonadotropin output but there is serious doubt that the high gonadotropin secretion is actually responsible for the symptom complex of the menopause It is of interest that estrogen relieves the hot flashes experienced by men who have undergone castration for carcinoma of the prostate [159]

Twenty five to 50 mg of testosterone propionate (LXXXIX) weekly [118] or 10 to 20 mg of methyltestosterone (XCVI) daily [119, 199, 200] has been reported to provide substantial relief in some patients but the proportion of those relieved is less than the proportion after estrogen Controlled statistical studies have indicated that 5 mg of methyltestosterone (XCVI) given orally t i d will give satisfactory control in 23 per cent of cases as compared to 97 per cent with 0 25 mg of diethylstilbestrol (CCXVI) t i d [178] Libido was more commonly increased with the androgen and nausea was less common Some degree of masculinization was seen in 13 per cent.

It would appear that androgens have no consistent over all advantage over estrogens in the routine control of menopausal patients One will encounter many women who because of the virilizing complications cannot tolerate large enough doses to achieve the desired result There are however several categories of menopausal subjects which are uniquely suitable for control by androgen rather than by estrogen One category is illustrated by the patient who suffers from uterine bleeding while receiving the minimal dose of estrogen which will control symptoms Androgen unlike estrogen causes no endometrial stimulation and hence no bleeding During the premenopausal interval when excessive uterine bleeding may accompany early appearing menopausal symptoms androgen is the preferred hormone for similar reasons Patients below the age of 60 or thereabouts who have had a malignant tumor removed from the breasts or uterus and in which therefore there is the possibility that estrogen may increase the growth of any residual metastases are also good candidates for androgen rather than estrogen Another example is the patient who has had *endometriosis* Endometrial implants may be *reactivated* by estrogen therapy after the recession following an artificial or spon

The early voice change consists of huskiness At this time there are hyperemia and swelling of the cords[117] If treatment is continued permanent fibrous thickening tends to supervene and the voice assumes the typical low pitched quality of the male Although the early voice change is reversible if treatment is long continued the structural alteration will not regress and the original feminine voice range can never be regained

Because of the considerable difference in individual susceptibility and the lack of extensive quantitative data no hard and fast rule can be laid down for the dose limit which if exceeded will lead to some degree of virilization The doses in Table 1 are approximate figures

TABLE 1

INCIDENCE OF VIRILIZATION WITH PROLONGED THERAPY

	Rare Occurrence or Slight	Appreciable Number but Minority Show Notable Effects	The Majority Show Distinct Effects
Testosterone propionate (LXXXIX)	100 mg per month	200 mg per month	[illegible]00 or above
Methyltestosterone (XCVI)	300 mg per month	600 mg per month	1200 or above

which have been formulated on the basis of the experience of others and of ourselves The dosages are not applicable if therapy is intermittent or of short duration For example 25 mg of testosterone propionate (LXXXIX) may be given daily to most women for as long as a week without any noteworthy complication Hair growth although one of the most troublesome side effects of androgen therapy requires weeks or months for its development

Kennedy and Nathanson[1] have made specific observations on the incidence of side effects from testosterone propionate (LXXXIX) in doses of *50 to 100 mg given three times a week for metastatic cancer* of the breast Within a month hirsutism and hoarseness were noted in 20 per cent of the cases After 7 months the incidence exceeded 90 per cent *Increased sex desire was apparent in 10 per cent of cases* after 1 month of therapy and in 50 per cent after 7 months The minimal expectancy of acne during such therapy was 30 per cent thinning of scalp hair 22 per cent ruddy complexion 44 per cent and edema 16 per cent

MENOPAUSAL SYNDROME Claims for the efficacy of the male hormone in the relief of menopausal symptoms made their appearance

ensue for 1 to 5 months in a small percentage of patients. These suppressive changes are reversible and do not appear to constitute a threat to subsequent fertility. If the dosage is kept between the limits of 10 to 20 mg. three times a week the control of bleeding is essentially as satisfactory as with the larger doses.[1, 124] Histological changes in the uterus are not in evidence and the menstrual cycle is not suppressed. The small dose regime possesses the added advantage of being below the threshold for any serious masculinization in most women. If bleeding is very active at the time therapy is instituted 25 mg. may be given daily for several days until control is achieved, after which smaller doses should prove adequate.

If the hormone is discontinued after several months of therapy about two out of three patients are reported to remain free from excessive bleeding for many months or perhaps indefinitely. Such a sustained effect is not necessarily dependent on any permanent alteration in the patient's endocrine status because similar "cures" frequently follow simple curettage or indeed may occur spontaneously. The frequency of relapse when myomata are present is considerably higher than in pure functional bleeding. When there is a tendency to recurrence or chronicity of bleeding, treatment with 10 to 25 mg. of testosterone propionate (LXXXIX) weekly may be continued indefinitely with good results in some cases.

Progesterone (XCIV) and testosterone propionate (LXXXIX) in daily doses of 10 mg. and 25 mg., respectively, for 4 to 5 days have been used together to terminate prolonged bouts of bleeding.[1] A short episode of secondary withdrawal bleeding is to be expected after such a course of treatment just as is the case after progesterone (XCIV) alone. In regular cyclic menorrhagia a similar course of injections may be repeated at monthly intervals before each expected period.

Although injected testosterone propionate (LXXXIX) has been used more extensively than other preparations, there is no reason to believe that oral therapy should not be satisfactory. A suggested oral dose of methyltestosterone (XCVI), for example, is 40 to 50 mg. daily until bleeding is controlled and 10 to 20 mg. daily thereafter. If given buccally the dose could be halved.

It goes without saying that careful gynecological and medical studies should be made in order to rule out a malignant tumor or organic disease before hormone is prescribed for uterine bleeding. It must also be admitted that a variety of other nonsurgical therapeutic agents aside from androgen may be used with good effect in functional bleeding. This is not a place for a discussion of their relative merits, how

taneous menopause Androgen does not stimulate but actually depresses such implants

Androgen and estrogen may be given in combination Doses of methyltestosterone (XCVI) ranging from 5 to 15 mg daily combined with 0 5 to 1 0 mg of diethylstilbestrol (CCXVI) *appear to* give a better subjective response than either hormone when given alone [178 1 9] Although estrogen alone is very effective in controlling *hot flashes the added androgen appears to give an improved sense* of well being along with increased sex interest In some patients because of troublesome uterine bleeding with the required amount of estrogen it is possible to reduce the dosage and yet maintain control of symptoms with supplementary androgen [*Example* 0 25 mg of stilbestrol (CCXVI) and 10 mg of methyltestosterone (XCVI)] It is also reported that larger doses of estrogen which ordinarily cause the complication of bleeding may be directly antagonized by the simultaneous administration of androgen [1 0 1 1] The intent is to neutralize the endometrial stimulation caused by estrogen Doses which have been used in such a regime are 1 to 3 mg of stilbestrol (CCXVI) and 5 to 25 mg of methyltestosterone (XCVI) daily

EXCESSIVE UTERINE BLEEDING The physiological effect of androgen on the human endometrium involves a depression of the growth and secretory activity of the epithelium and an inhibition of the development of the spiral arteries which control menstrual bleeding The mechanism of this action is considered to include a suppressive influence on the gonadotropin secretion of the anterior pituitary and probably also a direct inhibition of the endometrial tissue itself Although large doses are required to inhibit the pituitary it is not unlikely that a direct uterine effect may be attained with small doses In addition to endometrial effects an influence of androgen on the myometrium has been postulated although there is little of a physiological nature *to support such a concept in its application to the bleeding mechanism* of the uterus

In cases of excessive bleeding the hormone has been shown usually *to arrest or inhibit the flow no matter whether the bleeding is classi*fied as menorrhagic metrorrhagic or polymenorrheic Good results have been obtained at all age levels In the functional type of bleeding *up to 90 per cent of patients may receive substantial benefit* while the hormone is being given and an arrest of flow may be realized almost as frequently even if fibromyomata are present [12, 124] With doses as large as 25 *to* 75 *mg of testosterone propionate* (LXXXIX) three times a week given for 1 to 3 months histological evidence of endometrial regression is demonstrable and complete amenorrhea may

have been treated during the postovulatory phase (*10 to 14 days* before an expected period)[114, 129–131] The dose has varied from 5 to 25 mg *of testosterone proprionate* (LXXXIX) *two to three times* a week or 10 to 30 mg of methyltestosterone daily by mouth About three *out of four patients are reported to be completely relieved and in* some instances the effect is said to be sustained for several months after a course of treatment. Without careful statistical control having been employed in the various clinical studies which have been reported it is impossible to evaluate the contributions of suggestion and of spontaneous factors in bringing about the improvements as reported

ENDOMETRIOSIS Under the influence of estrogen the aberrant endometrial tissue is stimulated to grow and bleed in a manner resembling that of the normal endometrium Symptoms are therefore at a *maximum* before and during the menses Clinical observations indicate that under androgen treatment the aberrant tissue will shrink and the pain will be relieved in a high proportion of patients[116, 132] Moderate doses such as 25 mg of testosterone propionate (LXXXIX) two to three times a week or 20 mg of methyltestosterone (XCVI) daily given during the two weeks preceding a menstrual period may prove adequate to alleviate pain without the complication of significant virilization and without *abolition of menstrual flow* Methyl testosterone (XCVI) in daily oral doses of 10 mg and continued for *4 to 6 months may relieve dysmenorrhea and dyspareunia in 80 per* cent of cases This regime also seems to improve the impaired fertility[191] It has been reported that large doses (25 mg daily for 1 to 2 months) may result in an apparent permanent atrophy of the implanted tissue even though a regular menstrual rhythm is soon resumed after the termination of suppressive therapy[116] Treatment with androgen is particularly useful in cases where one wishes to avoid surgical intervention or where an artificial menopause is undesirable

PREMENSTRUAL TENSION Approximately half of all women experience some degree of premenstrual tension The usual complaint consists of various mixtures of nervous tension irritability emotional instability and depression Although the syndrome is undoubtedly based upon physiological alterations which accompany cyclic ovarian activity and is not primarily psychogenic nevertheless any psychiatric disorder may be concurrently aggravated There are other premenstrual phenomena such as edema or the intensification of allergic arthritic or dermal disorders which may or may not be due to the same underlying mechanism Various hypotheses have been proposed to explain premenstrual tension but evidence which might provide

ever mention might be made of the frequent *spontaneous* remission encountered frequently in young girls the occasional improvement with chorionic gonadotropin therapy at younger age levels the apparent benefit from thyroid administration in some cases the usefulness of a course of progesterone (XCIV) alone given before an expected period and the hemostatic effects of large doses of estrogen if administered while active bleeding is in progress Withdrawal bleeding after estrogen treatment may however be more severe than the original episode

DYSMENORRHEA Although in dysmenorrhea the painful sensation undoubtedly arises from uterine contractions the reason why pain occurs in certain individuals and not in others has not been satisfactorily explained Theories which have gained variable support include those which attribute the disorder to (1) an exaggerated force of rhythmic contractions or sustained elevation of muscle tone (2) anatomical defects of the uterus (3) increased local sensitivity within the pelvis—due perhaps to excessive hyperemia (4) a hypersensitive autonomic nervous system or (5) even a frank neurosis The principal cause probably varies among different patients There is no evidence of any hormonal aberration which might be incriminated However male hormone has been extensively tried for the relief of dysmenorrhea because of either an expected antagonistic or stimulative effect in relation to the action of endogenous estrogen and progesterone (XCIV) It should be remembered that a long list of unrelated drugs can be compiled which have been looked upon with favor for the relief of this condition so that one should not be criticized if he suspects that a response to any or all drugs and hormones may be mediated at least in part through psychological channels

If 25 to 50 mg of testosterone propionate (LXXXIX) are given three times a week throughout the month menses may be completely suppressed If such a dose regime is confined to the first two weeks after the onset of a preceding period ovulation is usually prevented (as with estrogen at this phase of the cycle) but a menstrual flow although often delayed is not always completely suppressed Such an anovulatory period no matter how produced is usually not accompanied by pain

The use of large doses of androgen as above introduces the hazard of excessive masculinization Clinical interest has therefore centered principally in the use of small submasculinizing doses Good results have been reported with 30 mg of methyltestosterone (XCVI) given daily during the 6 days before the expected time of ovulation [165] This dose does not appear to interfere with ovulation Patients also

to relieve frigidity Most patients have been observed for sex stimulating effects while receiving treatment for miscellaneous gynecological disorders or for breast cancer Table 2 combines a summary of

TABLE 2

EFFECT OF ANDROGEN ON SEX DESIRE IN WOMEN

Total Number of Cases	Previous Sex Interest	Distinct Increase	No Change	Decrease
38	Little or none	30	8	0
51	Normal	41	10	0
10	Excessive	1	8	1
31	Once normal and then lost	30	1	0

the published results in two of the larger series of reported cases [135, 136] Doses of hormone have averaged 10 to 25 mg of testosterone propionate (LXXXIX) three times a week 10 to 30 mg of methyltestosterone (XCVI) daily or 100 mg of testosterone (VIII) implanted in pellet form

Along with heightened sex desire there is usually easier attainment of orgasm and heightened satisfaction during intercourse Whether the influence of male hormone is mediated by direct action on the nervous system or by an enhanced sensitivity of the clitoral region or both is not clear If the clitoral sensitivity is of chief importance a local application of androgen in ointment form might suffice and would have the advantage of reducing the masculinizing hazards of therapy If dryness of the vagina occurs during androgen treatment and leads to dyspareunia the addition of estrogen ameliorates this side effect [136] In a certain proportion of patients who fail to respond, psychiatric factors are suspected of playing the major role In view of the fact that emotional disorders are a common cause of frigidity it is likely that if a series were compiled of women in which frigidity was the primary complaint the results would not be as striking as those indicated in Table 2.

The one instance in the table of excessive sex desire having been reduced by testosterone should be noted Such an effect is most likely to be obtained when the sex craving occurs premenstrually and is secondary to the emotional manifestations of premenstrual tension The decrease in sex urge after such treatment is probably dependent upon the relief of the nervous tension There are however several cases on record wherein nymphomania unrelated to the menstrual cycle has been relieved [137]

acceptance of any one of them is far from complete As an illustration of our confused state of knowledge androgen has been given by some clinicians because they hoped to antagonize a supposed excess estrogen level during the premenstrual phase whereas others have used it as a replacement for a presumed estrogen deficiency considered to occur at this time (analogous to its use in the menopause)

Whatever may be its mechanism of action androgen is effective against simple premenstrual nervous symptoms in the majority of instances The largest group reported is Freed's[133] consisting of 174 treated cases and 20 controls who received placebos Half the treated patients were completely relieved and less than 10 per cent unchanged About 10 per cent of the control group were completely relieved and half unaffected The relief provided by hormone is therefore derived from something more than simple suggestion

Small doses are effective A suggested regime consists of a total of one or two 10 to 25 mg injections of testosterone propionate (LXXXIX) or 10 to 20 mg of methyltestosterone (XCVI) daily by mouth during the critical 5 to 10 days before a period

FRIGIDITY Sex drive in the average woman is not as intense or compelling as it is in the average man moreover orgasm is not achieved with anything approaching the degree of certainty which is usually experienced by the male This difference is commonly thought to be due to the influence of custom training and moral pressure but there is evidence at present only suggestive that male hormone also may be of importance That is to say androgen in the human being may have a specific capacity to stimulate sex drive in both the male and the female When the existing level of circulating androgen in the female is augmented by the administration of extra hormone the direction of sex orientation is not changed for sex interest although often intensified remains heterosexual A noteworthy stimulation of sex drive in women by estrogen on the other hand is not very commonly encountered in clinical experience in spite of the fact that sexual receptivity in the female of lower animals is specifically controlled by this hormone

Perhaps the best proof of the existence of a specific effect of androgen on sex interest is the occurrence of heightened desire in cases where the hormone has been given for some other purpose and with the patient moreover unaware of the possibility of such a side effect Indeed this action was first noted as an incidental finding in studies which were concerned with the use of male hormone in the menopausal state[134] There is actually no great accumulation of data relating to the use of androgen in situations where the original intent was

ing two to three times a week during the latter one or two weeks before an expected period More than three fourths of the patients so treated usually experience relief of pain and premenstrual swelling[141, 144] An example of the response to testosterone is shown in Fig 3 Testosterone (VIII) ointment is likewise reported to be effec-

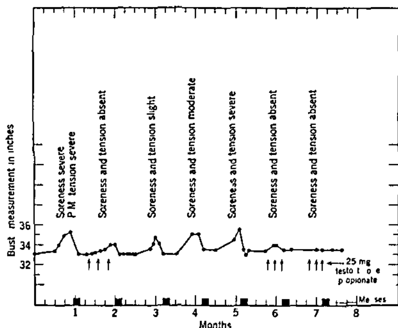


Fig 3 Effect of androgen on breast size and tenderness and on premenstrual tension in a 30 year old patient Methyl testosterone 20 to 30 mg a day for 10 to 14 days before a period was used subsequently with comparable results

tive when applied locally in daily doses of 2 to 5 mg for each breast[141, 145] The expectancy of relief with androgen is higher than the 50 per cent of patients who may experience subjective improvement with placebo therapy or no treatment at all A specific effect is also suggested by the relief observed in patients who were previously not benefited by other forms of treatment

NEOPLASMS *Uterine Fibroids* It has been noted in the foregoing section on uterine bleeding that the excessive menstrual flow which is frequently associated with uterine fibroids is often alleviated by androgen therapy There have been a limited number of observations concerned with the effect of such treatment on the size of fibroid tumors An apparent partial regression of palpable nodules has been

THE POSTPARTUM STATE Reports on the use of androgens for *painfully engorged breasts* are almost uniformly favorable Treatment is usually begun 2 to 3 days after delivery and is continued for 2 to 4 days Testosterone propionate (LXXXIX) by injection is effective in doses varying from 10 mg [138] to 30 mg [139] daily The expectancy of success is probably close to 90 per cent and substantial relief is usually achieved within 48 hours or less Methyltestosterone (XCVI) (50 to 100 mg daily by mouth) is equally satisfactory Dodek and co workers [102] recommend testosterone cyclopentylpropionate given as a single 100 mg dose during labor They consider the results better than those with any regime previously employed

Although the relief of engorged breasts is frequently referred to as inhibition of lactation milk production is actually not suppressed or even decreased by such therapy if suckling is allowed to continue [140] The therapy is most often used when the intent is either to interrupt nursing or never to start it Milk flow normally subsides when the suckling stimulus is absent irrespective of whether androgen is given or not The hormone however in some manner relieves the painful congestion which commonly accompanies the drying up process

Estrogens are just as effective as androgens in the relief of post partum congestion but occasionally they precipitate uterine bleeding

Doses of male hormone similar to those given above are also effective in the relief of *after pains* [138, 139]

BENIGN BREAST DISORDERS The disorder commonly known as chronic cystic mastitis may be subdivided into several separate varieties Two types seen frequently are adenofibrosis and nonpuerperal mammary secretion " [141] In the presence of these disorders there is frequently an intensification of pain along with a perceptible enlargement of the breasts during a 5 to 14-day interval immediately preceding the menstrual flow Many normal women experience similar symptoms during this phase of the menstrual cycle Consequently the differentiation between functional mastalgia and mild organic mastopathy may be difficult to make In both instances the premenstrual symptoms are thought to be due to vascular engorgement edema and glandular proliferation which follow upon the postovulatory augmentation of estrogen and progesterone secretion

Whether the disorder consists of true mastopathy or functional premenstrual mastalgia the severity of symptoms is highly variable from month to month and even a gross nodularity may undergo a spontaneous increase and decrease It is therefore difficult to evaluate the efficacy of specific therapy Testosterone (VIII) has usually been given as the propionate injected in doses ranging from 10 mg to 25

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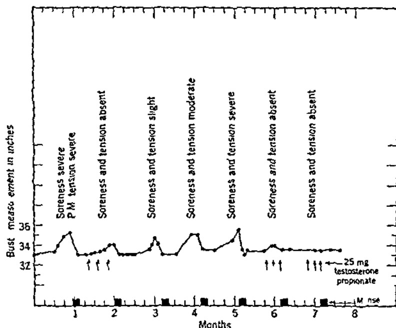


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observed in a certain number of cases however the tumors have not been abolished by such therapy and moreover the nodules tend to revert to their original size when androgen is discontinued The dosage which has been reported to affect a measurable shrinkage has varied from a total of 150 mg [146] (masculinizing dose) to 30 mg [147] of testosterone propionate (LXXXIX) a week in divided doses Testosterone propionate (LXXXIX) in pellet form (30 to 300 mg total) has also been shown to act similarly [148]

Carcinoma of Uterus and Ovary Testosterone has been given to patients with cancer arising from either the cervix or fundus of the uterus [149, 150] It has also been tried in cases of malignant tumors of the ovary [151] No evidence of alteration in the growth of these tumors has been forthcoming however a temporary gain in weight and an increased sense of well being have been noted in the majority of cases Testosterone is reported to have increased the responsiveness of carcinoma of the cervix to irradiation [156] No suppressive effects on metastases were observed in two cases of chorio carcinoma who were given 25 mg of testosterone propionate (LXXXIX) daily [83]

Carcinoma of the Breast For a surprising length of time after testosterone (VIII) was made available reports bearing on the treatment of metastatic cancer were confined to relatively small groups of patients and conclusions as to its efficacy if favorable were restricted to statements that the treatment showed promise After Fels [152] in 1944 described a dramatic regression of lesions in a patient who had been bedfast with widespread metastases there was an upsurge of interest and when additional excellent responses were reported by Adair and Herrmann [153] it began to appear that the hormone had attained a *foothold as a therapeutic agent in advanced cases usually* considered hopeless A large series has now been followed for a sufficient length of time to provide statistical data which may serve as a *guide to the clinician* [1]

Relief of pain improved appetite and weight gain may be expected within 3 months time in somewhat more than half the cases These effects are often observed whether or not the lesions progress Some degree of regression of osseous or soft tissue lesions is to be anticipated in about one out of five cases and the average duration of sustained improvement is 10 to 12 months In a small minority the inhibition of growth will persist for more than a year or two but the tumor is not obliterated and an ultimate fatal progression is to be expected In patients who respond the mean survival time is 11 months compared to 8 months for those who fail to respond The probability of

response is not significantly influenced by the age of the patient. Estrogen therapy, on the other hand, although statistically somewhat more effective than androgen in women well past the menopause, is less effective in premenopausal patients and not infrequently may stimulate growth of the tumor.

The accepted dose of testosterone propionate (LXXXIX) is 25 to 100 mg. three times a week. Larger doses are not more effective. Methyltestosterone (XCVI) given orally in doses of 200 mg. a day appears to be equally as satisfactory as injected testosterone propionate (LXXXIX). Various degrees of masculinization are of course to be expected. There is no evidence that other androgens such as methylandrostenediol (CXXXIII) or stanolone (XCVIII) possess relatively less masculinizing activity in relation to therapeutic potency.[193] Another complication which constitutes a distinct hazard is a tendency to occurrence of severe hypercalcemia in certain patients.[156, 157] This usually occurs within the first few weeks of therapy and necessitates withdrawal of hormone. Acceleration of tumor growth is occasionally observed and calls for termination of therapy.

Testosterone propionate (LXXXIX) in doses of 25 to 175 mg. a week has been tried postoperatively as a prophylactic measure against subsequent development of metastases.[158] Although the incidence of metastases appeared to be lower than would ordinarily be expected in this series, the longevity frequently attained without any postoperative treatment necessitates that a large series of cases be followed for a long period before such a regime can be properly evaluated. The masculinization which attends doses thought to be adequate deters the physician from adopting such a plan unless real benefit is to be expected. One criticism of prophylactic treatment is that cancer cells are not thereby destroyed but are induced to develop resistance to the hormone during a time when they are doing no damage. A subsequent spread of tumor would not thereafter be benefited by androgen.

The mechanism of action of androgen in effecting temporary inhibition of mammary cancer has not been established. Ovarian and possible adrenal suppression with the attendant decrease in estrogen formation might represent one important element in the over-all physiological reaction. It has been known for half a century that ovariectomy may sometimes lead to temporary regression of metastatic lesions and that it induces subjective improvement in one out of four cases.[15] It seems probable, however, that androgen has some action over and above that of ovarian suppression. Not only do the

statistics look better after androgen therapy than for ovariectomy but the response in elderly women would probably accrue from some thing over and above a theoretical suppression of the normally low estrogen level which exists at this age

Undesirable Side Effects of Androgen

In the preceding sections of this chapter certain unwanted side effects of the hormone are mentioned An example is masculinization of the female Additional complications which may arise in either the male or female merit further discussion

Salt and water retention

Male hormones like the cortical steroids tend to induce retention of sodium chloride (Chapter 14) If salt retention is excessive the augmented volume of the interstitial fluid is manifested as edema This complication although not rare is usually encountered only in those patients who receive doses in excess of 75 mg of testosterone propionate (LXXXIX) a week [83, 11, 113, 160, 161] A pre existing tendency to cardiac failure adds to the susceptibility and necessitates that the hormone be given with caution When it is desired to continue the hormone without a reduction in the dose the edema may usually be controlled by restriction of dietary sodium combined if necessary with injections of mercurial diuretic

An example of fluid retention as a result of overdosage in a patient is presented in Table 3 Except for eunuchoidism this boy was other wise normal

TABLE 3

EXCESSIVE ELECTROLYTE RETENTION IN A 24 YEAR OLD EUNUCHOID SUBJECT

Dat	W ght	Bl od I essu e	H a t S e (n)	M thylt to te (XCVI)	R k
October 194	149	110/70	12 3	N ne	N ed n
Dec 194	1 4			100 mg d ly f 2 k d 00 mg daily f 2 n w ks	No ed
J n 1943	15			100 mg d ily f th t m th	N ed
Feb 6 1943	162	145/85	13 1	100 mg daily f the p t m th	P tt g ed f a kl present
F b 2 1943	1 4	106 60	12	No d t n f t 3 week	N d n
J ly 1 1943	1 0	108 60		0 g daily fo t 5 nth	No ed

Depression of Spermatogenesis

Under certain experimental conditions androgen may be shown to suppress testicular function in lower animals (Chapter 11). In the human male normal sperm production may be strikingly reduced by testosterone (LVIII) even to the point of azoospermia.[5,11,162] The volume of seminal fluid is not greatly affected. Doses which have been observed to depress the sperm count range from 75 to 150 mg. of testosterone propionate (LXXXIX) a week and 75 to 200 mg. of methyl testosterone (XCVI) daily. The effect is not invariably present but will occur in 70 to 80 per cent of cases and is demonstrable within several weeks or less. When treatment is interrupted after 1 to 8 months the count has been observed to rise again in those cases which were followed. The action on the testis therefore appears to be reversible but it is uncertain whether prolonged courses of therapy might not ultimately be accompanied by irreversible damage.

Stimulation of cancer growth

Although there is no evidence that androgen can induce a malignant change if neoplasia of certain tissues is once established the hormone may stimulate the growth of the cancer. Thus carcinomatous tissue arising from the prostate is usually inhibited by castration whereas androgen therapy tends to promote growth and intensify pain.[1,8] Androgen is therefore contraindicated in the presence of prostatic cancer.

Cancer of the *male* breast likewise may be stimulated by androgen whereas it is dramatically suppressed by castration.[159]

Jaundice

Jaundice as a complication of therapy with androgen has been reported after methyltestosterone (XCVI) but not after testosterone propionate (LXXXIX) administration. The unusual hepatic change which produces the icterus is described in Chapter 19.

TABLE 4

SUMMARY OF CLINICAL USEFULNESS OF ANDROGEN THERAPY IN VARIOUS DISORDERS

Positive Indication; Response Invariably Good	Response Good; May Be Caused or Is Probably Due to Relatively Direct Hormonal Effect	Response Sometimes Observed but Element of Suggestion Undoubtedly Is Important	Response Sometimes Observed but Primary Disorder Probably Not Effected; Nonspecific Tonic Effect Is a Factor	Usefulness Not Yet Established or Evidence Conflicting although Favorable Effects Reported	No Clear-Cut Therapeutic Effect yet Established	Contraindicated
Primary hypogonadism Hypogonadism of pr d chronicity Male climacteric*	Undescended testes (gonadotropin treatment preferred) Pituitary dwarfism Panhypopituitarism Postmenopausal osteoporosis (with estrogen) Oligospermia Senile pruritus Adherence to f eskin Menopause† Uterine bleeding Endometriosis Premenstrual tension Postpartum breast engorgement Premenstrual breast engorgement Cancer of female breast	Prostatism Angina pectoris Enuresis Dysmenorrhea	Cushing's syndrome Cirrhosis of liver Involutional melancholia Muscular dystrophy Hyperthyroidism	Convalescence from chronic illness Premature infants Gynecomastia Renal tubular necrosis Cholera Simple senility Simple retardation of growth Frigidity of women as a primary complaint Uterine fibroids Addison's disease (as supplementary therapy)	Arteriosclerosis Nephrosis Nonhypogonadal impotence Homosexuality Cancer of uterus and ovary	Cancer of male breast Cancer of prostate

* Rebound after cessation of therapy
† As supplement to estrogen

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CHAPTER

19

Androgen Preparations and Methods of Administration

After the discovery that androgenic substances were present in urine, severe clinical trials of urinary androgens on hypogonadal patients were reported, both with crude extracts and with pure compounds. McCullagh[1,2] employed an extract ("androtin") containing 6 to 15 bird units per dose given every 1 to 2 days. An increased frequency *of erections was noted along with an improvement in sense of well* being and vigor. Kenyon obtained slight stimulation with dehydroepiandrosterone (XXIII) and androstane-$3\alpha,17\beta$-diol (XXXIV).[3] Urinary androgens, however, being limited in supply and weak in activity, never enjoyed wide clinical use.

In 1934 Kenyon treated a male hypogonad for 42 days with daily injections of a purified extract of bull testis supplied by F. C. Koch.[4] The total amount of hormone given to this patient represented the *yield from more than half a ton of testis; however, the dose* (1 to 2 mg. of testosterone equivalent per injection), we now know, was suboptimal and the response, although clear cut, was not striking by present day standards.

Fortunately a relatively simple partial synthesis of testosterone (VIII) was soon devised which made the hormone available in quantity. Otherwise the clinical use of male hormone would have been sharply restricted. Testosterone (VIII), testosterone propionate (LXXXIX), testosterone cyclopentnyl propionate (CLXVII) and methyltestosterone (XCVI) are the three androgenic preparations which are now used clinically. The choice of preparation depends largely on the *route of administration desired*.

Injection

Shortly after testosterone (VIII) was synthesized it was demonstrated that the free compound was less effective after injection than

some of its esters[4] Potentiation of activity by esterification may be attributed to retardation of absorption which promotes a more efficient utilization of the hormone The favorable effect of a slow delivery of steroid hormone has been well demonstrated in experimental animals[4, 14] Slow absorption of course also lengthens the duration of action An increase in length of the fatty acid chain up to a certain point causes a progressive increase in potency and duration of action If however the chain is made too long (palmitate and stearate) the

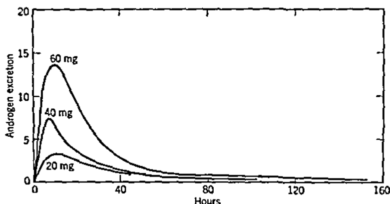


Fig 1 Duration of androgen excretion after a single intramuscular dose of testosterone propionate The values on the vertical scale represent international units per hour as determined by bioassay

activity declines (see Chapter 8) In clinical practice the propionic ester has enjoyed widest use as a preparation for injection

Testosterone propionate (LXXXIX) is marketed dissolved in oil An oily medium has certain practical shortcomings Rarely a patient shows true allergy to the vegetable oil Oil solutions should preferably be given intramuscularly because a subcutaneous injection may cause a local inflammatory reaction in some patients Absorption of the oil itself tends to be delayed until long after the hormone has been released and remnants often remain indefinitely as oil cysts There is no indication however that these deposits are harmful

The effect of a single injection of this preparation on the end organs of the rat is detectible for as long as two weeks[4] A *peak* effect occurs in about 10 days It should not be concluded however that these observations precisely reflect the rise and fall of hormone concentration in the body inasmuch as a lag in both the response and the regression of the end organ would be expected For efficient maintenance of end organs in the rat injections should be not more than one

week apart[46] Excretion studies in the human being indicate that the material is almost completely eliminated from the body within 2 to 5 days[5 80] (Fig 1) Thus for a sustained therapeutic effect in man it is preferable that the interval between injections should not exceed 4 to 5 days

An excretion of normal quantities of urinary androgen is not usually attained with doses of less than 20 to 25 mg daily[5 6] however this amount of hormone is not ordinarily necessary for a good clinical result For replacement therapy in hypogonadism 25 mg three times weekly is usually adequate and some patients are well controlled even with smaller doses

Other Preparations for Injection Free testosterone (VIII) has been administered to patients in an aqueous suspension[8] A preparation of this kind could theoretically be a very long acting one and therefore enable less frequent injections For example estrogens in aqueous suspension are much more slowly absorbed than when dissolved in oil *provided that particle size is not too small*[75] 17 Ketosteroid excretion has been seen to remain elevated 3 to 4 days longer after a single injection of suspended testosterone (VIII) than after a similar dose of testosterone propionate (LXXXIX) in oil[80]

Testosterone cyclopentyl propionate (CLXVII) in oil is unique as a long acting androgen[80 81] In the castrate rat not only will a single injection maintain the weight of the seminal vesicles for more than a *month but the magnitude of response is far greater than that resulting* from a comparable dose of testosterone propionate (LXXXIX) In hypogonadal patients one dose of approximately 200 mg given intramuscularly has been shown to provide relief of subjective symptoms for 3 to 4 weeks

Propylene glycol is a suitable solvent for steroid hormones and although *it may cause local irritation upon injection it is nontoxic*[9] In the experimental animal this vehicle is physiologically less efficient as a solvent for testosterone propionate (LXXXIX) than peanut oil[10 11] A solution of testosterone (VIII) in propylene glycol has been given to human subjects intravenously in doses as high as 250 mg without ill effects[76] However there appears to be no clinical advantage which favors *the routine use of this vehicle*

Methyltestosterone (XCVI) by injection is slightly more potent than free testosterone but is much less effective than testosterone propionate (LXXXIX) and therefore has no practical advantage when given by this route[11]

Percutaneous Administration

Animal experiments

Androgens were shown in early experiments to be absorbed through *the intact skin and to exert a strong action when applied locally to* the chick's comb [12] or to the penis of the castrate rat [13] An end organ is much more responsive to a small dose of steroid hormone applied *topically than to the same dose given systemically* Advantage may be taken of this in the performance of assays on test animals or in the clinical use of a hormone when it is desirable to minimize systemic effects [5] Nevertheless a systemic absorption of androgen (and other steroids) is demonstrable when larger amounts of hormone are applied to indifferent and remote areas of skin Thus it was early shown that genital stimulation followed upon application of androgen to the skin of the back of the rat [4, 16] In fact *free* testosterone (VIII) is *more effective when applied in this manner than after injection* The higher efficacy may be attributed to slower absorption through the skin with a consequent improvement in efficiency of utilization On *the other hand the potency of free testosterone (VIII) after inunction* is not equal to that of testosterone propionate (LXXXIX) after injection [11]

Testosterone propionate (LXXXIX) weight for weight is less active given by the percutaneous route than is free testosterone (VIII) [14, 15] Even if a correction is made for the weight of the inert propionate radical the esterified compound is somewhat less active than the free form [11] This may be due to the excessive retardation of absorption by the combined effects of the skin barrier and the esterification of the hormone Potencies of the compounds administered by the two routes in order of decreasing activity are testosterone propionate (LXXXIX) by *injection > testosterone by inunction >* testosterone by injection > testosterone propionate by inunction

Methyltestosterone (XCVI) is as active or perhaps slightly more active than free testosterone (VIII) when applied to the skin [11, 16]

Oily vehicles various ointment bases and alcoholic solutions have been employed as media for the cutaneous application of androgen Different ointment bases vary in efficiency and the several androgens also vary among themselves with different types of ointment A simple fat base is less suitable than special emulsified bases An alcoholic solution however gives results which are superior to those obtained with any of the ointments which have been tried [11, 17]

Clinical results

Foss[17] was able to produce clinical improvement in a human castrate by percutaneous therapy On the basis of stimulation of penile erections he estimated that testosterone ointment was one half to one fourth as effective as the same quantity of injected testosterone propionate (LXXXIX) For normal sexual potency 20 to 40 mg of testosterone (VIII) per day were required for inunction whereas 10 mg of testosterone propionate by injection would suffice There are several reports of submaximal clinical response with 12 5 to 25 0 mg of testosterone propionate applied to the skin by inunction daily[18-20] However demonstrable responses have been obtained with doses as low as 2 5 to 8 mg of free testosterone and 4 to 6 mg of testosterone propionate[21-24] It is fair to conclude that clinical results in general are in agreement with animal experiments in that androgen given by inunction is absorbed systemically but is not as efficient as injected testosterone propionate Data on patients are too meager to compare relative potencies as precisely as has been done with animals

Percutaneous administration has not found widespread use in clinical practice Although the patient is relieved of the necessity of injections the laborious and somewhat messy procedure of massaging an ointment into wide areas of the skin is not happily accepted (the usual sites employed are thighs and abdomen) In instances where a strong local effect is desired with minimal systemic action such as in disorders of the female breast inunction may sometimes be useful (Chapter 18)

Pellet Implants

Deanesly and Parkes[14] in studies on the rat showed that implanted compressed pellets of crystalline androgens were highly effective in maintaining the secondary sex organs Subsequent studies have confirmed that pellet implantation is from the physiological standpoint the most efficient method by which androgens may be administered[10, 11] It is highly efficient because absorption from the pellet is slow continuous and devoid of transient peaks which are wasteful of hormone Pellet implants yielding 3 to 5 mg of hormone daily are approximately as effective as 25 mg of testosterone propionate (LXXXIX) given three times weekly by injection Unfortunately the effective life of a pellet of testosterone (VIII) is much shorter than that of desoxycorticosterone acetate (CXXI) or estradiol 17β (L) Reimplantation at the required 3 to 4 month interval is objectionable to many patients even when done as an office procedure

Very large pellets with a longer effective life are difficult to implant and tend to extrude more readily

All three of the common androgens have been used in pellet form The superior potency of esterified testosterone (VIII) compared to the free form when administered by injection does not hold for pellet therapy This may depend upon the fact that the absorption rate of free testosterone in pellet form is already slow enough to provide an efficient utilization of hormone so that further retardation by esterification is of no advantage Animal experiments suggest that the efficacy *per milligram of absorbed hormone* is similar for testosterone methyltestosterone (XCVI) and testosterone propionate (LXXXIX) [11, 25]

Rate of absorption

Free testosterone (VIII) is absorbed most rapidly and testosterone propionate (LXXXIX) least rapidly whereas methyltestosterone (XCVI) is intermediate In addition to this difference among the compounds it has been established that the rate of absorption varies directly with the surface area of the pellet [32, 42] Absorption appears to proceed chiefly by slow dissolution at the exposed surface thus the larger the available surface the greater will be the daily yield of hormone A certain degree of permeation of tissue fluid into the body of the pellet occurs but it is unlikely that the central core of a reasonably well compressed pellet gives up an appreciable amount of hormone The internal texture of a pellet is not visibly altered when it is removed after many months in situ and moreover it has been shown that fused pellets are absorbed at essentially the same rate as compressed pellets [26] Absorption is greatly retarded by the mixing of cholesterol with the active steroid [30]

The rate of dissolution is not constant during the entire period that the pellet remains in situ In general as surface area decreases the rate of hormone delivery declines [40, 42] A flat type of pellet shows less diminution in area as it loses mass than does a cylindrical type [32] and therefore maintains a more constant rate of hormone supply until final dissolution In general however no matter what the shape the decline in absorption rate is not extreme until 80 to 90 per cent of the pellet is gone [31] A roughening of the surface which develops may for a time offset the loss in area due to shrinkage in mass and thus maintain a rate of absorption close to the original value By systematic implantation of "booster doses" a very uniform rate of delivery may be achieved [42]

Table 1 is a summary of data obtained from the literature on rates of pellet absorption in relation to pellet weight and type of androgen. Rate of absorption does not seem to depend to any great extent on sex, type of subject (whether animal or man) or physiological requirement. Neither is there any very marked difference between implants in muscle or in subcutaneous tissue.

TABLE 1

RATE OF ABSORPTION AND DURATION OF ACTION OF PELLETS

Hormone	Micrograms per Sq. Mm. Absorbed per Day	Pellet Weight (mg.)	Per Cent Absorbed per Month	Milligrams Absorbed per Day per Pellet	Effective Life of Pellets (months)	Estimated Number of Pellets Necessary for Replacement Therapy in Man
Testosterone (VIII)	6–9	<5	>90	<0.1	<1	>[illegible]0
		30–50	40	0.5	2	8–15
		75–225	30	1.5	3	3–6
Methyltestosterone (XCVI)	4–5	<5	>90	<0.1	<1	>50
		5–10	70	0.[illegible]	1	25–50
		40–100	30	0.7	3	5–12
Testosterone propionate (LXXXIX)	3–4	<10	60	<0.[illegible]	<2	>25
		20–50	24	0.3	4	15–30
		100–300	16	1.0	5	4–10

Absorption rate has been estimated on the basis of observations reported for the initial half to three-fourths of the life span of the pellets.[5, 11, 14, 2, 25, 1] Due to the widely divergent sources from which the above averages were compiled and the many gaps in available data, this table is intended only as a rough guide. Values for per cent absorption in relation to pellet weight are particularly subject to variation because of differences in surface area of the many types of pellets which have been used.

Tissue reaction

A mild foreign body reaction occurs around an implanted pellet and leads to the development of a thin fibrous capsule in which are enmeshed moderate numbers of foreign body cells, lymphocytes and a few polymorphonuclear leucocytes. No severe tissue reaction is to be expected in the majority of cases, and simple asepsis prevents any infection.

Methods of implantation in man

Pellets may be implanted in the subcutaneous tissue or subfascially onto the muscle layer. Subcutaneous implantation is simpler and gives perfectly satisfactory results. In an early technique a 2 to-3 cm incision was made and the requisite number of pellets simply de

posited in a single large pocket which had been dissected open either under the skin or under the deep fascia With this method a large space filled with fluid and invested with a common capsule sometimes forms around the group of pellets In another technique which would seem to be preferable individual pockets radiating from the incision are made with a hemostat and one pellet is placed in each pocket By this method as many as ten moderate sized pellets may be inserted through a single incision

If pellets are of cylindrical shape it is possible to insert them sub cutaneously by means of a trocar [43] or if they are very small by the use of a large gauge needle Special injectors have been devised [8, 44] in cluding one for the insertion of the 75 mg pellet (Oreton Schering) which is available on the market * The Kearns pellet injector may be thrust through the skin without any incision and the pellets deposited either in a continuous line or in separate pockets In that consider able force may be required to penetrate the skin and underlying tissue the procedure may be facilitated by an initial small incision followed by a preliminary loosening of the subcutaneous tissue with a hemostat as described above

Regions which have been chosen for implantation include the infra scapular area posterior axillary line thighs abdomen and scrotum The scrotum offers no advantage as a site An occasional complica tion is the spontaneous extrusion of pellets after an interval of several weeks This may be avoided by placement as far as possible from the edge of the incision One centimeter or more should be allowed be tween the edge of the pellet and the wound

Oral Therapy

Testosterone and its esters

Early investigators observed that testosterone was relatively ineffec tive when given by mouth Suspicion arose that the compound was either not absorbed or was inactivated by the enzymes in the gut Neither of these two hypotheses could be proved but it was shown by Dorfman and Hamilton that *testosterone (VIII) is in fact absorbed* from the gut and that its metabolites may be recovered in good yield from the urine [45] The clinical efficacy of oral testosterone in a case of eunuchoidism was however estimated to be only one sixth that when given by injection Foss [17] also using clinical criteria estimated

* Kearns Pellet Injector H Laurent & Co Inc. 18 Columbia St Newark N J

the ratio to be 1 20 Assays in rats by Emmens and Parkes [46] indicated a ratio of 1 10 The low efficacy after oral administration is now ascribed to hepatic inactivation [47] After absorption by the gut the hormone must pass through the liver before reaching the systemic circulation The process of inactivation consists of a conversion to less active compounds (such as androsterone) along with a chemical conjugation with sulfate or glycuronate radicals (Chapter 5)

Methyltestosterone

POTENCY Miescher and Tschopp in 1938 discovered that methyltestosterone (XCVI) was considerably more active when given by mouth than testosterone [48] The clinical practicability of oral androgen therapy was soon established [49] It would appear that the unique superiority of methyltestosterone for this purpose is due at least in part to a higher resistance to hepatic inactivation [50] This is not to say however that the compound completely escapes significant degradation It has been established that the efficacy of this androgen given orally is only two fifths that attained after injection of the same compound [46] This degree of efficiency however is approximately four times that of testosterone (VIII) given by mouth and is of sufficient magnitude to make oral therapy economically practical The convenience to the patient is obvious

Many reports testifying to the clinical efficacy of methyltestosterone (XCVI) in hypogonadism have appeared [18-20 36 49 51-62] All the androgenic effects of testosterone (VIII) are well duplicated The relative potency of the compound given by mouth as compared to testosterone propionate (LXXXIX) given by injection would appear to be roughly 1 to 3 or 4 In other words the dose must be three to four times as high to achieve the same results For replacement therapy this would be equivalent to 20 to 50 mg per day A tabulation of clinical estimates of dosage is given in Table 2

It should be noted that in some conditions other than frank hypogonadism it has been reported that oral methyltestosterone (XCVI) has not given results as satisfactory as those attained with parenteral testosterone *propionate (LXXXIX) There is such a claim in the* treatment of senile pruritus [63] Heller and Meyers [64] obtained poor results in the therapy of the male climacteric although Werner [65] observed a satisfactory clinical response in this condition

SIDE EFFECTS Methyltestosterone (XCVI) is not a naturally occurring hormone and is metabolized in the body in an atypical fashion It is not converted to androsterone or similar metabolites and therefore does not lead to an appreciable rise in 17 ketosteroid excretion

Its administration is also attended by a substantial increase in creatine excretion (Chapter 14) One would therefore wonder whether the compound might produce side effects not encountered with testosterone (VIII) Occasional instances of mild gastric "fullness" or discomfort have been described which may be relieved with antacids (Table 2) Edema may be produced with *high doses* but this property is

TABLE 2

OPTIMUM DOSAGE AND OBSERVED SIDE EFFECTS OF METHYLTESTOSTERONE (XCVI) IN THE TREATMENT OF HYPOGONADISM

Dose Range (mg per day)	Average Effective Dose	Relative Dose as Compared to Injected Testosterone Propionate (LXXXIX)	Side Effects Observed in Some Patients	Ref
40				18
5 100	30		Occasional gastric discomfort	20
10–75		2 or 4 to 1	Occasional gastric discomfort	36
30–100			Occasional slight nausea	49
25–150		3 or 4 to 1		51
25–75	50	2 5 or 3 5 to 1		52
100–150				53
75				54
50–100	50	4 or 6 to 1	Occasional gastric irritation	55
25–300	75	7 to 1		56
20–30		3 or 4 to 1		57
50–150				58
60–80				59
40–80				60
20–50				61
30–100				62
20–60	30		Occasional heartburn and muscle cramps	63

shared by testosterone (VIII) and all steroids which cause sodium retention (Chapter 14) Jaundice has been described during methyl testosterone (XCVI) therapy[79, 82] This does not appear to be connected with hypersensitivity is not accompanied by parenchymal damage and is not related to the sex of the patient the size of the dose or the duration of treatment The histological change which is easily reversible after stopping the hormone consists of a curious stasis and plugging of the bile capillaries

Sublingual and Buccal Therapy

The discovery that desoxycorticosterone (CXXI) is effective when given sublingually[66] led to similar trials with other steroid hormones. The animal experiments of Miescher and Gasche[67] indicated that methyltestosterone (XCVI) was twenty to thirty times as potent sublingually as when given by stomach tube. This extreme difference is difficult to explain in view of subsequent clinical reports and in light of the fact that it would appear to make methyltestosterone more effective sublingually than after injection. Lisser and co-workers[68] obtained stimulation in hypogonadal patients with solutions of testosterone (VIII), methyltestosterone and testosterone propionate (LXXXIX) in propylene glycol. Two tenths of a cubic centimeter of solution containing 5 mg of hormone was placed under the tongue two to five times daily. The effects seemed to be somewhat better than with a similar quantity of methyltestosterone when swallowed but were not so good as would be expected with 25 mg of testosterone propionate injected three times weekly. In a subsequent study slowly soluble 5 mg tablets of methyltestosterone (Ciba Linguets) were used by Lisser's group instead of the propylene glycol solution.[0, 78] This method was preferred by the patients and the clinical results pointed to a clear-cut superiority of the sublingual route over the oral. Other workers have reported similar experiences.[71, 74] As now employed, the tablets are most often used in a buccal position, i.e., in the groove between the lower cheek and the gum. The dose requirement is approximately one half to one third of the oral dose, and for replacement therapy in hypogonadism 5 to 30 mg a day are required. Although free testosterone and its esters also are effective sublingually,[69] they appear to be less potent than methyltestosterone.[76]

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CHAPTER

20

The Excretion of Androgens and 17-Ketosteroids in Various Clinical Conditions

During the last decade a large body of data has been made available on the excretion of 17 ketosteroids and the biologically active group of compounds termed androgens Because of the availability of a relatively simple chemical method most studies have been concerned with 17 ketosteroids The usual difficulties of bioassay have prevented the accumulation of any extensive data on androgens It has been pointed out in Chapters 4 and 7 that urinary androgens and related 17 ketosteroids are a complex mixture of different steroids which consist of metabolic end products from multiple hormonal precursors secreted principally by the adrenal cortex and testis It must again be emphasized that the quantitation of these compounds as a group is not a specific measure of the function of either organ Much overlap exists between ranges of excretion found in health and in most disorders of the adrenal cortex and testis to say nothing of disease which primarily involves nonendocrine organs

The excretion of androgens and 17 ketosteroids in the urine is influenced both by the basal status of the individual and by the stressing conditions to which he is subjected Variables pertaining to the basal status include the usual determinants such as age developmental level and sex Stressing conditions may be broken down into two categories namely long range processes of disease and short range stimuli such as physical activity and emotional stress which are the result of the individual s physical and psychical contact with his environment The 17 ketosteroid excretion at any time is the resultant of all these operating factors Most of our attention will be focused on the effects of age sex sustained nonendocrine illness and of specific endocrine disorders This chapter is essentially a compendium of most of the reported assays of 17 ketosteroids and androgens in normal and abnormal subjects

The Normal Subject

Influence of sex

MEN The concentration of androgens in the urine of normal men has been determined by bioassay in a number of different laboratories The summary in Table 1 indicates that in a given laboratory a variation of threefold to tenfold may be encountered between subjects giving highest and lowest values The variation in mean values from laboratory to laboratory is between 19 and 99 I U per day and of individual values as low as 10 I U to as high as 225 I U The wide discrepancy in averages among various laboratories may be explained in part by differences in completeness of extraction and in the extent of chemical alteration during hydrolysis For example it may be recalled that if during hydrolysis androsterone (XXV) the principal androgen of urine is converted to $\Delta^{2,3}$ androstene 17 one (LII) a tenfold loss of androgenic activity results

17 Ketosteroid values for normal men also are summarized in Table 1 In 19 studies Callow's[67] method was used In 7 of these reports the mean uncorrected total neutral fraction varied from 13 3 to 18 4 mg per day with an over all average of 14 6 In 12 other reports wherein either the ketonic fraction or the total neutral fraction after color correction was employed the over all mean was 13 8 mg per day (variation from 7 6 to 20 0 mg) The Holtorff and Koch technique[58] has yielded values higher than those found by the Callow method[67] A mean excretion varying from 15 3 to 22 6 mg per day has been found when the total neutral fraction was assayed. The over all mean derived from the various reports is 17 2 mg The ketonic and corrected total neutral fractions by the Holtorff and Koch method has an over all mean of 12 7 mg per day for five studies The use of the micro method of Drekter et al [14] which involves a determination of the total neutral fraction has yielded average values varying from 15 0 to 18 0 mg per day and an over all mean of 16 6 By the polarographic method the mean is seen to be 15 9 mg per day (variation from 15 7 to 16 8 mg)

WOMEN Studies on the excretion of androgens and 17 ketosteroids in the urine of normal women are presented in Table 2 without regard to time of the menstrual cycle since no significant correlations have been reported The extreme range for androgens is 5 to 85 I U per day although some earlier workers have reported values even lower than 2 I U The averages from different laboratories vary from 14 to 47 I U

TABLE 1

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(NORMAL YOUNG MEN)

Number of Subjects (Age Range)	17 Ketosteroids				Androgens		Ref
	Method	Remarks	Range (mg /day)	Mean (mg /day) ± S E	Range (I.U. /day)	Mean (I.U. /day)	
					19–48		7
4 (6 55)					115	66	8
7 (?0-44)					?0– 5	99	9
13 (20–40)	C	T tal tral corrected	9 8–?0 8	14			11
9 (?0–40)	C	T tal tral cor ected	8 1 6	13 8			1
	C	T tal n tral corrected		13 8			13
?0 (3–37)					16–86	39	14
10 (?0–40)	C	T tal ne t al	11 6–1 5	14 3			15
11 (1 30)	C	T tal n tral MgO	10 5–19	14 1			16
14 (0–36)	H & K.	T tal n tral	15 9–34 0	2 6			17
?3 (4–42)	C	T tal ne tral cor ected	6 7 27 2	12 5			19
46 (?0–60)					?0–121	50 (pprox.)	?0
12 (?0–51)	H & K.	T tal tral corrected	10– 5	17 0			21
27 (20–45)	C & S.	T tal utral	3 1 23 0	14 2			22
4 (0–30)	P	Total utral	18 8–21 0	15 7 ± 2 5			53
8 (20– 2)	P	T tal neutral	12 7 5	16 8 ± 9			54
8 (?0–)	C	T tal tral		18 4 ± 4 7			54
5 (3–3)					10–	19	94
14 (?0–40)	C	Total ne tral co ected	6 0–?0 8	13 6			144
20 (?0–40)	C	K tone	5 4– 1 2	11 4			14.
11 (0– 9)	H & K	T tal tral (prison rs)	5 9–1 5	10 8			106
9 (30–39)	H & K.	T tal eutral (prison rs)	5 2 20 0	10 1			
5 (24–30)	H & K	T tal tral	10–21 0	15 3			
24 (?0–30)	H & K.	T tal eutral	13 4–27 0	19 8 ± 3 5			107
12 (19–3)	?	T tal tral	9 1 13 8	11 4 ± 1 7			108
6					40–140	8	109
3 (–37)	C	K tone	6 8 5	7 6			110
40 (20–40)	H. & K	Ketone MgO	4 9–18 4	10 2			111
26 (?0– 5)	C & W	T tal ne tral	5 4–18 5	11 4			112
16 (1 28)	C & W	T tal n tral	4 3–21 0	9 5			113
	C	T tal ne tral	12 18				114
	C	T tal n tral	9 4– 0 9	13 3			38
5 (21 34)	C	T tal n tr l	5 1 19 3	12 7			115
20 (20–40)					17 104	37	111
16 (16 + ?)	H & K	K ton	10 0 6	14 7 ± 1 6			118
8 (?0–30)	C	T tal t al corrected	5 5– 5	14 4			11

[C t next page

TABLE 1 (*Continued*)

Fxcretion of Androgens and 17 Kftostfroids

(Normal Young Men)

Number of S bjects (Age Range)	1 Ketoster ids				Androg ns		Ref
	M thod	Remarks	Range (mg /d y)	M an (mg /day) ± S F	Range (I U /d y)	Mea (I U /day)	
18 (30–40)	C	T tal eutral corr ted	7 0–22 5	13 5			
7 (3 36)	H & K	T tal eutral	11 2 30 5	18 1			1 1
10 (20–38)	P	Total utr l	10 4 21 8	15 3			1 8
11 (31–40)	C	Total eutral corr cted		16 8 ± 2 2			13
1 (0–30)	H & C	T tal eut al	14 5–29 5	21 0			89
18 (30–40)			11 0–35 0	0 9			
53 (1 34)	D	Total t l	9 0–30 0	18 0			146
11 (35–49)	D	T tal neutral	7 0– 3 0	15 0			146
19 (0–60)	H & K	Total tral	10 0– 3 2	16 2			148
14 (0–58)	C & S	T tal tral	8 5–23 0	15 9			1?0
24 (19–30)	C & S	Total neutral	13 1 27 1	19 8			150
10 (.0–40)	C	T tal tral	11 6–17 5	14 3			90
9 (18–41)	T & O		9 2 0 2	16 7			151
14 (?0–51)	H & K	T tal tral rrected	10 0– 5 0	16 6			153
44 (0–49)	H & K	T tal e tral	4 0–24 0	11 5			75
7 (0– 9)	J	T tal e tral		13 6			168
12 (30–39)	J	T tal tral		20 3			168
15 (40–50)	J	T tal tral		16 0			168
35 (0–.0)	D	T tal tral	10 0– 8 9	16 9			147
18 (?0–30)	C	T tal tral	6 7 19 1	15 6			1 6
18 (30–40)	C	Total tral	7 5–19 6	13 4			1 6
18 (40–50)	C	T tal e tral	4 3–12 5	7 1			1 6
6 (0–35)	R	T tal eutral	19 8– 5 0	21 6			1 8
23 (1 –63)	H & K	K tom tral	5 0–18 8	9 4 ± 0 6	25 0–86 4	43 ± 4	189
54 (19–43)	H & K	Ketom tral		12 0 ± 0 6			191
29 (18–41)	C	T tal tral orr ted	9 9–31 3	.0 0			33

C & W = Ch d Wu method [2]
C = Call w et l method [57]
H & K = H lto ff d Koch method [58]
C & S = C h d Salte method [22]
P = P lar gr ph metl od [53]
S E = Standard e f an
D = D kte et al [147]
T & O = Tomps tt and Oestle [1 2]
J = Jaylo et al [162]
R = R I l d C I [177]

C l l t d f m h ly tp t gl t [189] day [191]

TABLE 2

LXCRETION OF \NDROGENS AND 17 KETOSTEROIDS

(NORMAL WOMEN)

\ mber f S ibj cts (Age Ra ge)	17 ketoster ds				A d ge		Ref
	Method	Re arks	Range (mg /day)	M an (mg /d y) ± S.F	Ra g (I U d y)	M (I U day)	
5 (.3-39)	C	T tal utral	5 4-19 6	12 2			.0
15 (20-40)	C	T tal utr l corr ted	5 8-17 0	10 2			11
14	C	Total neutral orrected	5 1 14 2	9 0			12
8 (.0-26)					20-68	41	9
4 ( )-34)					22 85	47	8
					50		5
					7 35		6
9	C	T tal t al or ted		9 1			13
5 (1-43)	Os	T tal n tral	3 0- 8 0	i 6			6
3	Os	Total n ut al	4 3-17 3	9 5			24
4 (26-38)	C	Total n t al MgO	3 8-4 8				16
30 (20-40)	H & K	Total ut l	4 0-22 0	12 6			17
65 (23-37)	C	T tal neutral corrected	3 8-18 9	8 2			19
.0 (0-60)					5-84	18	20
12 (1 38)	H & K	Total ne t al rr ted	7 0-18 0	11 0			21
13 (39)	C & S	T tal n ut al	5 2 14 0	8 4			22
0 (19 37)	P	Total n utral	5 3-18 1	11 9 ± 3 8			54
.0 (19-37)	C	Total utral	6 2 22 4	13 2 ± 4 8			54
5 (?0-35)	C	Total ut al	5 6-15 5	10 1			15
3 (30-36)	C	Ketonic	4 1 3 6	5 0			110
6					18-80	44	109
18 (20-40)	H & K	K tonic MgO	1 5-9 7	7 0			111
6 (0-60)					0-48	14	100
6					)-30 C L	42 C U	27
	C	?	3 5-14 6	7 4			38
36 (16 + ?)	H & K	Keto	5 5-21 4	8 7 ± 1 6			118
0 (0-30)	C	T tal t l cor ected	4-16	10 0			117
15 (30-40)	C	T tal eut l corre ted	2 5-9 0	5			
31 (20-40)					8-80	4	?0
10 (18-24)	P	Total utral	8 5-21 4	14 1			1 8
	C		1 7 12 6	6 8			10
18 (0-35)	C	Total e tral co rected	4 8-1 0	10 0			144
13 (0- 9)	J	T tal utral		9 5			163
19 (30-39)	J	T tal utral		8 8			
12 (40-49)	J	T tal tr l		9 4			
6 (.0-40)	R	T tal ne tral	6 6-9 8	6 2			178
11 (0-51)	H & K	K to n tral	2 2 14 9	6 7 ± 1 2	3 34	16 3 ± 0 2	189
(18-46)	C	T tal ut al or ected	4 4 2 5	10 9			2 3

C = Call t al method[37] H & K = H ltorff d Koch method[1]
Os = Oest g method.[3] C & S = Cohe and Salter method[23]
P = F larogr phic method[53] J = J yl et al[1]
R = Robles and G bson,[177]

Calc lated from h urly o tput o night

TABLE 1 (*Continued*)

Excretion of Androgens and 17 Ketosteroids

(Normal Young Men)

Number of Subjects (Age Range)	Method	Remarks	17 Ketosteroids Range (mg./day)	Mean (mg./day) ± S.E.	Androgens Range (I.U./day)	Mean (I.U./day)	Ref.
18 (30–40)	C	Total n tral orrected	0–2 5	13 5			
7 (3 36)	H & K	Total neutral	11 ? 30 5	18 1			121
10 (20–38)	P	T tal e tral	10 4– 1 8	15 3			1 8
11 (31–40)	C	Total neutral rected		16 8 ± 2 2			132
12 (0–30)	H & C	Total neutral	14 5–29 5	21 0			69
18 (30–40)			11 0–35 0	0 9			
53 (17 34)	D	T tal neutral	9 0–30 0	18 0			146
11 (35–49)	D	Total tral	7 0–23 0	15 0			146
19 (0–60)	H & K	T tal eutral	10 0–.3	16 2			148
14 (0–58)	C & S	Total neutral	8 5–23 0	15 9			1?0
24 (19–30)	C & S	T tal tral	13 1 2 1	19 8			150
10 (0–40)	C	T tal tral	11 6–17 5	14 3			90
9 (18–41)	T & O		9 2 ?0	16 7			151
14 (0–51)	H & K	T tal neutral corrected	10 0– 5 0	16 6			153
44 (?0–49)	H & K.	T tal n utral	4 0–24 0	11 5			5
7 (?0–29)	J	T tal ne tral		13 6			168
12 (30–39)	J	Total neutral		?0 3			168
15 (40–50)	J	T tal eutral		16 0			168
35 (20–30)	D	T tal eutral	10 0–28 9	16 9			147
18 (?0–30)	C	T tal tral	6 7 19 1	15 6			1 6
18 (30–40)	C	T tal tral	7 5–19 6	13 4			1 6
18 (40–50)	C	Total tral	4 3–12 5	7 1			1 6
6 (0–3.)	R.	T tal e tral	19 8–25 0	1 6			1 8
23 (1 –63)	H & K	K tom tral	5 0–18 8	9 4 ± 0 6	.5 0–86 4	43 ± 4	169
54 (19–43)	H & K	K ton eutral		12 0 ± 0 6			191
9 (18 41)	C	T tal tral corrected	9 9–31 3	?0 0			.33

C & W = Ch w and W m thod [8]
C = Call w t al m thod [57]
H & K = H lto ff d Koch method [58]
C & S = C he and Salte m thod [22]
P = P larogr ph method [53]
S.E. = Standard e or f mea
D = Drekter et al [147]
T & O = Tompsett a d Oe tl [152]
J = Jaylo et al [162]
R. = R b d C leon [177]
C l lat d from h ly tp t g t [189] day [91]

metabolites in the urine are chemically similar and sometimes identical the parent substances of the former are weak androgens or inactive whereas in the latter the parent hormone testosterone (VIII) is extremely active The adrenal therefore although contributing perhaps two thirds of the total urinary metabolites is a minor contributor to the blood of physiologically potent androgen

Influence of age

CHILDREN During the first year or two of life children excrete but very small amounts of 17 ketosteroids and androgens (Tables 3 and 4)

TABLE 4

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(GIRLS)

Age (years)	Androgens (I U /day)	17 Ketosteroids (mg /day)					
	Ref 6	Ref 3	R f 4	Ref 5	Ref 86	Ref 154	Ref 181
3-4	0 3 (2) †	1 2 (1)		2 ~ (6)	Trace		0 6 (3)
4-	2 8 (2)	- 0 ( )		3 0 (5)			1 2 (8)
5 6	1 0 (2)			3 0 (4)	0 4		1 4 (6)
6-7	1 8 (2)	2 9 (1)		3 7 (5)	0 5		3 0 (9)
7-8	2 0 (3)	3 6 (2)		4 4 (14)	1 0		3 2 (6)
8-9	5 0 (2)	5 8 (1)		6 0 (4)	1 3		4 0 (7)
9-10	3 4 (2)			5 0 (4)	1 2		5 5 (17)
10-11	7 0 (7)	6 8 (1)		7 6 (5)	2 2	3 3 (9)	7 2 (15)
11-12	9 0 (4)		2 3 (7)	10 3 (6)	3 0	3 6 (9)	8 4 (10)
12-13	8 0 (6)	6 5 (3)	3 2 (9)	10 2 (5)	4 5	3 7 (6)	8 7 (5)
13-14	18 0 (5)	12 0 (1)	6 1 (9)	8 0 (3)	4 5	4 5 (4)	11 0 (4)
14-15	15 0 (1)	10 5 (4)	6 2 (7)	11 6 (3)		4 4 (4)	12 8 (4)
15-16			7 5 (10)		8 2	5 9 (5)	13 4 (3)
16-17			7 , (1)				
1 18					10 0		

Values stimated from plotted data (color correction employed)
† Numbers in parentheses ndicate number of subjects

After this time the two undergo only a gradual increase until after the age of 7 to 9 when the curve steepens (Fig 1) It is apparent from the data in Figs 1 and 2 that no significant difference between the sexes is evident before puberty Between the ages of 10 to 12 the status

Numerous studies of 17 ketosteroids in the urine of normal women have been reported In studies utilizing the method of Callow et al[52] mean values varying from 10 1 to 13 2 mg per day have been re ported for the uncorrected total neutral fraction and from 5 0 to 10 9 mg for the ketonic fraction The grand average for the tot il neutral fraction is 11 8 mg and for the ketonic fraction 9 1 mg With the Holtorff and Koch method[58] the over all average for the ketonic frac tion is 8 3 mg per day as compared to 12 6 mg for the total neutral component The polarographic method was used in two studies and mean values of 11 9 mg and 14 1 mg were found

It is a striking fact that the difference in hormone excretion in the two adult sexes is relatively small when compared to the extreme anatomical sex differences This however is understandable if one remembers that the steroid metabolites which reach the urine are at most a very crude reflection of the quantity of biologically active an drogen initially elaborated Thus although the adrenal and testicular

TABLE 3

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(BOYS)

Age (years)	Androg n (I U d y)	1 1 tost j (g / las)						
	R f l a d	R f 3	R f 4	R f	R f 8	R f 1 4	R f 1 6	R f 181
4 8 †	0 3 (2) ‡							
2 3	1 0 (1)				0 2			
3–4	1 0 (1) 1 3 (1)	2 4 (4)		3 0 (4)				
4–5		2 4 (4)		3 3 (5)	0			1 (3)
5–6		2 4 (3)		3 6 (4)			2 5 (4)	2 8 (7)
6–7		5 (4)		3 7 (9)	1 5		5 (4)	0 (4)
7 8	1 0 (1)	4 1 (3)		5 1 (6)	T a e		2 (4)	2 6 (4)
8–9	4 0 (4)	4 9 (4)		5 3 (8)	0 6		(4)	3 9 (3)
9 10	8 0 ( )	8 2 (2)		7 8 (2)	0 8		3 (5)	5 0 (4)
10–11	5 0 ( )	8 (3)		7 (3)	2 0	3 3 (8)	2 5 (10)	7 6 ( )
11–1	7 0 (16)	6 2 (2)	1 8 (9)	11 1 (4)	3 6	3 2 ( )	2 4 ( )	9 3 (7)
12–13	11 0 (11)	9 6 (1)	3 4 (6)	13 2 (3)	3 5	3 0 (10)	4 6 (5)	11 0 ( )
13–14	9 0 (d)	10 4 (6)	6 3 (11)	13 2 (2)	3 8	3 (11)	4 6 ( )	13 1 (4)
14 15	11 0 (30)	10 8 (4)	6 9 (8)	15 9 (5)	4 3	7 3 (8)	4 7 (5)	14 1 ( )
15–16	0 (32)	14 4 (1)	7 6 (8)		0	7 2 (8)	6 8 (5)	16 1 ( )
16–1	0 (23)		8 5 (7)		8 5			
17 18	25 0 (3)				8 0		9 3 ( )	
0– 2	3 0 (3)							

* V l e est mated f o pl tted data (l t pl y l)
† D ys
‡ N mbers n par theses dicat number f bj t

been demonstrated in the growing child[73] The relative increase in 17 ketosteroids in males over females after puberty is usually attributed to the contribution of the maturing testes It is of interest however that the adult male adrenal is larger than that of the female and body size is likewise greater An augmented adrenal component therefore also could contribute to the divergence which occurs after puberty

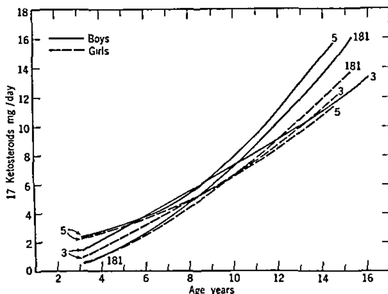


Fig 2 17 Ketosteroid excretion in childhood Numbers accompanying the smoothed curves indicate references from which data were obtained

OLD MEN AND OLD WOMEN From the reports on the concentration of androgens and 17 ketosteroids in the urine of old men it is evident that as age advances there is a decrease in these urinary constituents (Table 5) Whereas one laboratory reports a mean value of andro gens of 99 I U per day for men 20 to 34 years of age a mean of 20 I U per day was found in a group of six men 59 to 67 years old[9] In two other studies men of the age group 50 to 76 years were reported to excrete one seventh to one tenth of the amounts excreted by young men In an extensive study by Hamburger et al it was found that men 50 to 60 years of age had androgen values only slightly de creased from those of young men (Table 5) In the 60 to 70 year age group however the value dropped to one third and in the 70 to 80 year group it was down to one fourth

tical divergence characteristic of adult life first becomes detectable Ultimate adult levels are not reached until adolescence is completed Thus Mason s laboratory[4] obtained an average 17 ketosteroid excretion *of 8 5 and 7 5 for boys and girls respectively at the age level of 16 to* 17 whereas the corresponding values for adults were 14 2 and 10 2 mg per day[12] The findings of Talbot[88] and Hamburger[117] are similar

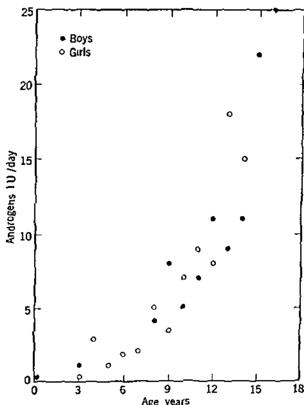


Fig 1 Androgen excretion in childhood Data from references 1 and 2

For androgens *determined by bioassay* values after age 20 also are higher than during adolescence (Tables 1 to 4) It should be remembered that the curves of Fig 2 are derived from composite values and represent the over all pattern of the groups studied The curve of an individual child may deviate considerably

In the prepuberal period 17 ketosteroids probably are derived almost entirely from the adrenal cortex The rise in hormone excretion with increasing age may represent nothing more than the growth and development of this gland along with the increment in body mass as a whole A correlation of 17 ketosteroid and creatinine excretion has

been demonstrated in the growing child[73] The relative increase in 17 ketosteroids in males over females after puberty is usually attributed to the contribution of the maturing testes It is of interest however, that the adult male adrenal is larger than that of the female and body size is likewise greater An augmented adrenal component therefore also could contribute to the divergence which occurs after puberty

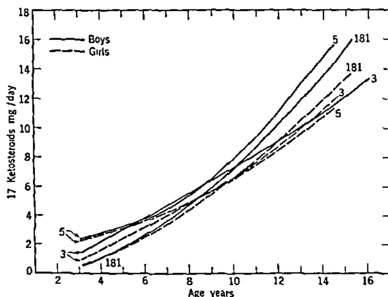


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TABI E ɔ

Excretion of Androgens and 17 Ketosteroids

(Old Men and Old Women)

Numl er of Subje ts (Age Range)	17 Ket st r id			Andr g ns			Ref
	Rang (g /day)	Me n (g /d y)	Auth r M an Yo g Adult Val e n g /d y (R ng)	Ra g (I U /day)	Mean (I U /day)	A th or M n Yo g Ad lt V lue I U /day (Ra ge)	
			M				
(50-76)				2 3		(19-48)	8
1 (9)							9
1 (87)				10-2	18	99 (20-22)	9
6 (ɔ9-67)				ɔ-40	20	99 (0-2 5)	9
5 (71-7)	8 4 3	3 4	13 8 (8 1 6)				12
4 (82-88)	9 12 0	5 9	2 6 (15 9 34 0)				17
1 (62)	6 3 12	9 4	22 6 (15 9 34 0)				17
? (7-81)		10 0	10 5 (2 20 0)				1
10 (50-59)	3 6 10 7	6 0	10 5 (- 0 0)				106
7 (60-69)	3 8 6 9	4 8	10 5 (5 0 0)				
3 (70- 5)	2 1-4 0	9	10 5 (5 2 0 0)				
5 (olde)				6 17	9	19 (10-2)	94
6 (60-70)	6-16 0	10 0	22 6 (1 9 34 0)				116
16 (70-80)	3 4-18 8	8 8	2 6 (15 9 34 0)				
12 (80-9)	3 17 6	8 7	22 6 (15 9 34 0)				
13 (0-60)	4 5-13 0	9 1	14 0 (5 5 5)				11
11 (F0 0)	2 0-8 0	0	14 0 (5 5)				
12 (0-80)	? 0-8	3	14 0 (5)				
13 (80-90)	2 0-6	4 1	14 0 (5)				
3 (90-10)	2 7-4 0	3 6	14 0 ( )				
30 (61-92)		3 8 ± 0 4	6 0 ± 0 f				191
19 (50-60)	3 0-10 3	6 0	14				1 0
14 (60- 0)	3 3-7 8	5 4					
12 (70-80)	1 6-5 0	3 8	(6 19 6)				
5 (80-90)	0-3 0						
9 (ɔ0-60)				5-7	43	50 (20-121)	20
1 (60-70)				C 30	16		
6 (0-80)				8	1		13
2 (ɔ0-60)		7 7 ± 0 8	16 8 ±				
8 (60 0)		7 8 ± 0 6	16 8 ± 2 2				

TABLE 5 (*Continued*)

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(OLD MEN AND OLD WOMEN)

Number of Subjects (Age Range)	17 Ketosteroids			Androgens			Ref.
	Range (mg/day)	Mean (mg/day)	Authors' Mean Young Adult Value mg/day (Range)	Range (I.U./day)	Mean (I.U./day)	Authors' Mean Young Adult Value I.U./day (Range)	
1 (0-80)		6 4 ± 0 9	16 8 ± 2 2				
2 (80-90)		4 3 ± 0 9	16 8 ±				
12 (50-59)		12 0	16 6				1[illegible]8
6 (60-69)		9 6	16 6				
3 (45-)	7 6-8 7	8 2	21 6 (19 8-2 0)				1 8
3 (55-65)	4 1 8	4 9	[illegible] (19 8 25 0)				178
3 (6 -7)	3 0-3 6	3 3	21 6 (19 8- 0)				1 8
[illegible] (50-60)		8 8 ± 0 7	15				184
[illegible]9 (60- 9)		7 0 ± 1 0	15				
31 (70 80)		5 3 ± 0 6	15				
8 (80+)		4 3 ± 0 [illegible]	1				
13 (40-59)					4	40	7
4 (60-7)					7		
Women							
(65-72)				9-11	10	41 (0-68)	9
1 (4)		6	11 0 (7 0-18 0)				[illegible]
1 ([illegible])		6	11 0 (7 0-18 0)				
5 (50-60)	3 8-7	6 5	7 8 (4 0-16 0)				117
12 (60 0)	0 9-6	3 3	7 8 (4 0 16 0)				
1[illegible] (0-80)	1 0-6 0	3	7 8 (4 0-16 0)				
13 (80 [illegible])	0 9-4 2	1 9	7 8 (4 0-16 0)				
6 (50 60)				2 11	7	4 (8-50)	0
1 (0-80)	4 0 12 4		1 6 (4 0-22 0)				116
(80-85)	4 1 8 5	6 3	12 6 (4 0- 0)				
8 (50 9)		8 6	9 2				1[illegible]8
17 (60-[illegible]9)		6 3	9 [illegible]				
9 (70-79)		9	9 2				
3 (50-60)	4 -4 9	4 5	8 2 (6 6-9 8)				1 8
3 (60-80)	2 7 3 4	3 0	8 2 (6 6-9 8)				
41 (40-49)		6 1	8 6				6
44 (50-59)		5 6					
7 (60-69)		4 2					
66 (0 9)		3 9					
51 (80-)		2 7					

A number of laboratories have reported on the 17 ketosteroid excretion in older men (Table 5) Three reports are particularly noteworthy In young men Hamburger[117] found the excretion to average 14 mg per day At 50 to 60 years of age it dropped to 9 mg and beyond age 80 it ranged from 2 to 3 mg In a similar study by Heller[116] the urinary titer of men over 60 years of age was approximately 40 per

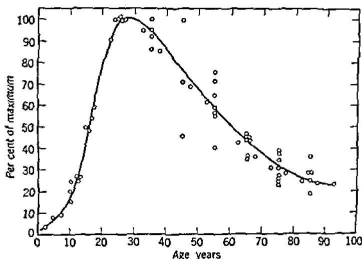


Fig 3 17 ketosteroid excretion in relation to age (males) The smoothed curves have been drawn through plotted points derived from data in publications which present assays on young adults in addition to those of children and older age groups

cent of that of young men Hamilton and Hamilton[106] found a small decrease in men of the 50 to 60 year old group and a drop to about 45 per cent in men 60 to 70 years of age The titer at 70 to 75 years of age was down to about one fourth In the series studied by Wooster[75] the first significant decline in excretion did not occur until after the age of 50

It is apparent from Table 5 that women experience the same decline in androgens and 17 ketosteroids in old age as do men After the age of 80 the output may decline to about one fourth of that seen in young adults

The rise and fall of 17 ketosteroid excretion from birth to senility is illustrated in Figs 3 and 4 Although composite data of this kind necessarily must suffer from considerable scatter the trend is unmistakable Highest output is encountered between the ages of 20 and 30 in both men and women The contour of the curves is similar in the two sexes Although Hamburger's[117] series revealed a tendency

toward temporary flattening of the curve for the female group between the ages of 35 and 50 other reports have not as yet confirmed this finding The decline observed in old men could be due in part to a decrease in gonadal androgen secretion however this is certainly not the case in women for it will be noted later that ovariectomy is not characteristically attended by a fall in output It is difficult to avoid

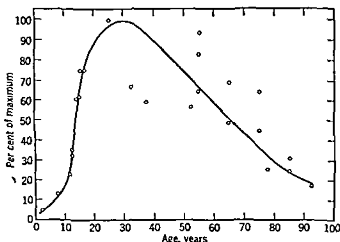


Fig 4 17 ketosteroid excretion in relation to age (females) Scatter between the ages of 30 and 50 introduces considerable uncertainty as to the true contour of the curve

the conclusion that a diminution in the adrenocortical contribution in both sexes is of considerable importance in the causation of the depressed excretion in senility

Short Term Stresses

Physiological stress

Pincus [74] has studied diurnal variations in 17 ketosteroid excretion At night during sleep the output varied from 0 25 to 0 80 mg per hour (ketonic fraction) as compared to 0 35 to 1 30 mg per hour immediately after rising A gradual decline then occurred during the day Wooster [5] and Forbes [19] have made similar observations In the latter study male subjects who excreted 15 2 mg during an 8 hour waking period put out only 11 9 during a like period of sleep The corresponding values for women were 9 0 and 7 5 mg

Under conditions of psychosomatic stress where rigid alertness and precise muscular coordination are required as in the operation of a

pursuit meter or in piloting aircraft increases of 50 to 100 per cent have been observed [74] The well known occurrence of lymphopenia and eosinopenia during emotional stress points toward a similar augmentation of 11 oxygenated adrenal steroid secretion The rise of 17 ketosteroid excretion is probably an end result of the outpouring both of preformed 17 ketosteroids and of other corticoids such as hydrocortisone which are degraded in part to 17 ketosteroids

In that 17 ketosteroid excretion is so easily altered by physical activity emotional status and certainly many unknown factors it is not surprising that a moderate fluctuation is encountered in the 24 hour output of normal subjects Thus Werner [78] obtained the following values for the ketonic fraction during a month s survey of the daily fluctuations of three subjects

Average	Low	High
11 2	6 0	14 2
15 0	10 1	17 3
10 2	6 9	12 2

Although most daily samples did not vary more than 2 to 3 mg either from the basal average or from the preceding and following days an occasional very low value was encountered and the extreme range from high to low was quite marked Albright s laboratory has made similar observations [1 19] Talbot reported that a single 24 hour determination deviated from a subject s true average by no more than ±15 per cent in two thirds of the instances whereas a deviation of ±30 per cent was never exceeded [86] (See also reference 117) Single *24 hour samples are therefore usually adequate for clinical purposes*

Forced diuresis and fluctuations in urine volume seem to exert no consistent influence on 17 ketosteroid output [74 6] Drugs such as Carinamide and Benemid sharply reduce the excretion [200 04] These steroids are therefore eliminated at least in part by active tubular secretion Although Gardner and co workers [20] could detect no difference in the ratio of androsterone and dehydroepiandrosterone while Benemid was given the excretion of neutral reducing lipids was uninfluenced Thus all steroid compounds are not affected equally

The menstrual cycle is not normally accompanied by a fluctuation in the level of 17 ketosteroid excretion [5 9] In the publication by Sanfilippo [189] twenty normal women between the ages of 12 to 53 were studied at days 1 7 14 21 and 28 of the cycle The mean 17 ketosteroid values were 6 9 6 8 6 8 6 7 and 6 7 respectively In contrast to normal subjects lowered values have been reported during

the time of menstrual flow in cases of dysmenorrhea[77] and increased levels near the time of ovulation in hirsute women[192]

Injury and nonspecific disease

Physical stress which results from trauma (operative procedures burns) or infection usually causes a characteristic alteration in keto steroid excretion[19, 12, 13, 281, 58] *There is at first a moderate increase* (circa 50 per cent) but after several days a sharp decline ensues and

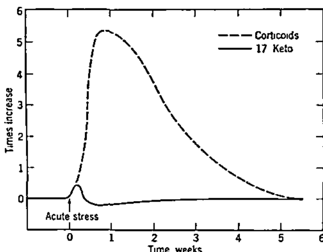


Fig 5 Schematic representation of the adrenal response to stress

levels then remain for a time at about three fourths of the original value If the stress is prolonged as in debilitated patients suffering from any chronic illness the low level of excretion persists (see Table 24) and if a new acute stress is superimposed the patient remains resistant to any *further rise or fall in the already low level*

These changes in 17 ketosteroid excretion during stress are considered to be due to the response of the adrenal cortex to the reaction of injury Selye[79] was the first to point out the probable importance of the gland in this connection ("alarm reaction" "adaptation syndrome) Albright[80] also has discussed its clinical implications Figure 5 is a rough graphical presentation of the two hormonal alterations which accompany acute stress The data for "cortin" excretion were obtained both from our own observations[81] and from those of others[62, 63] It is noteworthy that the ketosteroid changes are minimal in comparison to the elevation in cortin like material The initial transient elevation of ketosteroids during the first phase is not accom

panied by any significant nitrogen retention The picture is dominated throughout by the secretion of C_{21} 11 oxygenated adrenal steroids by the gland rather than C_{19} androgens and the over all reaction of the body is predominantly that of protein catabolism along with the other physiological responses to cortical hormone

Irradiation both ultraviolet and x irradiation appear to increase the excretion of 17 ketosteroids Myerson and Neustadt[250] exposed male patients (in depressive state) to irradiation from a quartz lamp which emitted 52 per cent infrared 20 per cent luminous and 28 per cent ultraviolet rays Urinary 17 ketosteroid assays (author refers to these as androsterone or sex hormone assays) were performed before and after exposure Exposure of the chest resulted in an increased steroid excretion but less than could be elicited by exposure of the genital region X irradiation (350 roentgens) produced an increased 17 keto steroid in dogs in the experiments of Laurence [1] although Duffy [5] could not demonstrate a change In a more extensive study Lau rence [53] showed that urinary excretion of 17 ketosteroids increased significantly between the fifth and twelfth day following exposure to a minimal lethal dose of 1100 kv total body x irradiation The rise was followed by a fall to normal or subnormal values

Profound changes in 17 ketosteroid excretion have been observed during morphine withdrawal from addicted patients[254] During addic tion the 17 ketosteroid excretion was decreased (about 55 per cent) and within 24 to 72 hours after withdrawal of the drug it rose from 60 to 500 per cent During this time the eosinophil count fell to nearly zero and significant increases were found in the uric acid creat inine ratios The 17 ketosteroids returned to the control levels dur ing the third and fourth week after withdrawal These changes point to an intense adrenal cortical activation

The stress of migraine headaches causes a significant increase in 17 ketosteroid excretion[255] Young men subjected to periods of wake fulness for 112 hours did not show significant changes [6]

Starvation

After four days of starvation normal subjects showed a decrease of about 50 per cent in both androgen and 17 ketosteroid excretion[84] In twelve young men who were subjected to total starvation and hard physical work during a 4 day period the 17 ketosteroids dropped to 3 6 mg per day as compared to the control level of 11 4 mg[108] In another group ten normal men who lost 13 to 24 per cent of their original body weight over a 2 to 6 month period of semistarvation showed a reduction to about two thirds of the control values

Various "Constitutional" Conditions

Women with dark hair and skin have been found to excrete larger quantities of 17 ketosteroids and androgens than light colored subjects [85] Excretion in the adult has been reported to manifest a positive correlation with body stature and creatinine output [75] Forbes to the contrary could demonstrate no such correlation with either height weight complexion or creatinine excretion [19] Simple obesity in children does not affect the output [86] Children who exhibit simple precocity in somatic and sexual development will anticipate the higher level of excretion ordinarily expected at an older age Hormone output thus corresponds more closely to developmental status than to chronological age [1 39 86] The reverse is seen in cases of retarded sex development

Among prisoners who have committed violent crimes the output has been found higher than in those incarcerated for nonviolent crimes [75] *There are two reports which present evidence of a relatively low* 17 ketosteroid excretion or low ratio to estrogen in homosexual males [87 88] Sevringhaus and Chornyak [121] however found no statistical difference in output between a group of homosexual males and a series of normal controls Somewhat higher 17 ketosteroids and lower estrogens have been found in male subjects who are judged psychologically highly masculine by standard masculinity femininity tests [89] If correlations of hormone excretion with psychological and emotional variants are verified by further careful statistical work the facts will be of considerable biologic interest Even then however *one could by no means conclude that the mental and emotional status* of a person is necessarily a result of the magnitude of male and female hormone production Establishment of a positive correlation does not constitute proof of causal relationship

Clinical Disorders

Eunuchoid and castrate men

Table 6 is a summary of urinary assays on eunuchoid men ranging in age from 18 to 56 years A relatively large variation in androgens and 17 ketosteroids is apparent Thus androgen levels from below 1 I U per day to 66 I U per day have been reported and 17 ketosteroid levels of 1 mg to more than 15 mg per day However the *values for androgens and ketosteroids average from one third to one* half of the value normally expected.

TABLE 6

Excretion of Androgens and 17 Ketosteroids

(Eunuchoid Men)

Number of Subjects (Age Range)	17 Ketosteroids			Androgens			Ref
	Range (mg./day)	Mean (mg./day)	Author's Mean Normal Adult Value mg./day (Range)	Range (I.U./day)	Mean (I.U./day)	Author's Mean Normal Adult Value I.U./day (Range)	
11 (18-35)	4 8 5	4 J	13 8 (8 1 2 6)				1
3 (39-56)	5 6 13 3	9 4	9 1	5-66	31		25
1 (40)		5 4	17 0 (10-25)				1
5 (19-41)	0-6 0	5 1	10 2 (4 9-18 4)				111
3 (18-36)				4 16	9	37 (17 104)	111
8 (6-36)				0-33	19	66 (12 115)	29
9 (20-5)				0-14	8	37 (17 104)	31
(18-4)				9 7	19	66 (115)	30
8 (1 45)	1 4-15 7	8 3	22 6 (15 9-34 0)				17

Castrate men still excrete androgens but the amounts are even lower than those for eunuchoid men The mean excretion is of the order of 10 I U per day or one sixth that of normal men (Table 7) No apparent correlation has been observed between the titer of androgens in the urine and the time since castration The few values reported for 17 ketosteroids indicate quantities of the order of that found for eunuchoid men

Castration in cases of prostatic cancer has been found to result in an ultimate slight rise in ketosteroid excretion[90] These aging men had preoperative values which were lower than in young males The postoperative rise could be attributed either to an improved state of health which allowed the adrenal cortex to contribute more than enough to compensate for the loss of testicular androgen or perhaps there was overcompensation on the part of the adrenal to the withdrawal of testicular secretion It is of interest that the frequent recession of prostatic tumor in such cases bears testimony to a decline in physiologically active androgen in circulation in spite of the rise of

TABLE 7

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(CASTRATE MEN)

Number of Subjects (Age Range)	17 Ketosteroids			Androgens			Ref
	Range (mg /day)	Mean (mg /day)	Author Mean Normal Adult Value (mg day)	Range (IU day)	Mean (IU day)	Author Mean Normal Adult Value (IU d)	
2 (1 56)				1 3 8	3 8	66 (7 115)	79
11 (-6)				6- 1 8			3
3 (4 64)				0 16	6	3 (1 104)	31
9 (19-46)	5 0 10 9	7 7	9 0 (3 5-15 0)	7 8	17		[illegible]
4 (43- 6)				3-11	8	66 (?? 115)	60
4 (45-)				4-13	8	37 (17 104)	111
5 (4 -6?)	1 4 6 0	3 3	10 2 (4 9-18 4)				111
3 (47 66)	3 0	5	13 8 (8 1 22 6)				12
10 (8-60)	3 -9	6	14 0 (5 5-3 5)				117
10 (6- 5)	1 8-16	6 6	14 3 (11 6-1)				15

urinary 17 ketosteroids Estrogen therapy causes a drop in 17 keto steroids [88] however clinical results are not superior to those obtained by castration

Hypogonadal and ovariectomized women

Values which have been obtained in hypogonadal women (exclusive of menopause) are presented in Table 8 Primary ovarian agenesis is accompanied by values averaging about half normal The reason for this depression in 17 ketosteroids is not clear In two series of patients with primary amenorrhea there is a slight decrease In patients whose menses once established have ceased before age 40 there is no change in one series [1] and a substantial elevation in the other [71]

Hamblen and co workers have encountered rather high values for 17 ketosteroids in women after ovariectomy and also after the natural menopause (Table 9) [18] The average for these subjects was 6.5 to 9 3 mg per day as compared to a normal mean of 3 4 mg The patients

TABLE 8

Excretion of Androgens and 17 Ketosteroids
(Female Hypogonadism and Menstrual Disorders)

Diagnosis	Number of Cases	Mean 17 Ketosteroids mg./day (Range)	Author's Mean Normal Adult Value mg./day (Range)	Remarks	Ref
Ovarian agenesis dwarfing high FSH	[illegible]	(Androgens) 2 5 I U	47 (2 85)		46
	11	4 (2–6)	9 ([illegible]–14)		67
	5	2 (1–4)	4 (1 9)		68
	4	5 (3–6)			69
		9 (6–19)	(12 18)		[illegible]0
Never menstruated poor sex maturation	3	6 (5–)	9 ([illegible]–14)	Low FSH	[illegible]
	7	5 (2–3)	3 4 (1 5–)		[illegible]1
Premature cessation of menses	7	9 (5–14)	9 ([illegible]–14)	Low FSH	[illegible]1
	17	7 (3 10)	3 4 (1 5–5)	FSH not reported	[illegible]
Men[illegible]	10	3 6 (1 6)	3 4 (1 5–)	D[illegible] 2 18 y	71

TABLE 9

Excretion of Androgens and 17 Ketosteroids After Ovariectomy or the Menopause

(Age under 60)

Androgens

Type of Cases	Time Since Ovarian Failure	Number of Cases	I U per day: Mean and Range	I U per day: Young Adult Mean and Range	Ref
Ovariectomy	1 mo to [illegible]7 yr	16	20 (1–135) *	(2–[illegible]0)	2[illegible]
Ovariectomy	1 year	3	9 (<6–12)	(30–60)	9

17 Ketosteroids

Type of Cases	Time Since Ovarian Failure	Number of Cases	Mean and Range	Young Adult Mean and Range	Ref
Ovariectomy	1 to 2 yr	[illegible]	8 9 (4 9–11 9)	9 0 (5 1–14 2)	12
Ovariectomy	1 mo to 4 yr	[illegible]	7 1 (5 0–21 4)	6 7 (1 7–12 6)	[illegible]
Ovariectomy	7 mo to 16 yr	7	6 5 (3 8–10 1)	3 4 (1 5–4 7)	18
Natural menopause	5 mo to 5 yr	[illegible]	[illegible] 3 ([illegible] 1–13 [illegible])		

* Many of these assays are reported as milligrams per liter rather than per 24 hr

in Callow's group showed no clear cut elevation[25] Albright's laboratory likewise obtained values after ovariectomy which were no different from a series of normal women[1] Since all the subjects in Table 9 were assayed one month or more after any surgical procedure the effect of acute stress is not involved A rise in androgen excretion determined by bioassay has not been demonstrated after ovariectomy[9, 5]

Although the foregoing series of patients is small and statistical evaluation unsatisfactory the following conclusions seem justified Ovariectomy and the natural menopause cause no fall in ketosteroid values There may be a variable degree of elevation under such circumstances, but a well marked effect is not consistently encountered Scrutiny of the curve of excretion with advancing age in Fig 4 shows no indication of a rise near the age of 50

Addison's disease

In Addison's disease there is a well marked depression of androgens and 17 ketosteroids (Table 10) In males the androgen excretion is approximately one half of normal and 17 ketosteroids range from one third to one fifth of normal In females there is a comparable reduction in androgens and 17 ketosteroids are less than one fourth of normal Albright's laboratory finds that ketosteroids are virtually absent in the female and it is pointed out by this group that such would be anticipated if the ovary produces no precursors of these compounds[1] This apparent absence of 17 ketosteroids is predicated on the application of a correction factor for interfering chromogens An equally precise estimate of true 17 ketosteroid chromogens may be obtained by use of the ketonic fraction for the color reaction When this was done on our own series of cases[17] the values were lowered but did not reach zero It should also be noted that androgen is detectable by bioassay in the urine of female Addisonian patients[25] Thus although body levels of ketosteroids and androgens in the female with Addison's disease are distinctly low they are not uniformly absent

Pituitary abnormalities

Panhypopituitarism results in extremely low or virtually absent 17 ketosteroids in both the male and the female (Table 11) This may be attributed to combined atrophy of the adrenal cortex and the gonads With the loss of both sources of these steroids in the male the resulting excretion is of course even lower than in Addison's disease or hypogonadism

TABLE 10

Excretion of Androgens and 17 Ketosteroids

(Addison s Disease)

Number of S bjects (Age Rang)	1 Ketosteroids			And ogens			Ref
	Range (mg /day)	M an (g /day)	Author s Mean Young Adult Val mg /d y (Range)	Ra g (I U /d y)	M (I U /day)	A thor s Mean Y ung Adult Value I U /d y (Rang)	
M							
9 (1 34)	1 3-12 0	8 5	2 6 (15 9-34 0)				17
3				7 3	16 0		5
3 (33 58)	2 1 3 5	7	13 8 (8 1 2 6)				12
1 (28)		3 1	17 0 (10-25)				21
7 (adult)	0 9-8 8	3 8	14 7 (10 7 0 6)				118
6 (24-51)	1 7-4 0	7	10 (4 9-18 4)				111
7 (-54)				3-19	10 0	37 *(17 104)*	111
11 (18-51)	1 9-4 4	3 3					83
1 (2)		7	15 (8 5-23 0)				1 0
2 (40-50)	4 5-7 1	5 8	1 6 (19 8- 5 0)				1 9
36 ( )	1 0-8 0	4 2	15 0 (8 0- 3 0)				149
W m							
5 (3-64)		0	9 0 (5 1 14)				1
5 (adult)	1 4-10 2	5 1	8 (5 5 11 4)				118
5 (3-40)	0-8 7	5 4	16 (12 3)				119
7 (33-49)	1 0-2 1	1 4	7 0 (1 5 9)				111
3 (9-56)	3 1 4 9	4	11 0 (7 0-18 0)				1
4 (?0-5)	0 2 2 6	1 0					83
5 (19-57)	1 5 3 6	9	8 4 (5 14 0)				1 0
4 ( )	1 3 0	7	8 2 (6 6-9 8)				1 9
3 (8 34)	1 1 2 7	f	(*11*)				*104*
3 ( )	0 1 8 6	3 0	10 0 (5 0-12 0)				149
4 ( )				11 6	18		5
(30-38)	1 3-4 4	3 1	12 6 (4 0- 0)				17

O case was also a un ch.

TABLE 11

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(PANHYPOPITUITARISM)

Number of Subjects (Age Range)	17 Ketosteroids				Ref
	Range (mg./day)	Mean (mg./day)	Author's Mean Normal Adult Level mg./day (Range)	Remarks	
Men					
1 (49)		2.0	9.1	Androgens (0.8 I.U./day)	10
1 (18)		0.6	14.2 (9.8–20.8)		11
1 (30)		1.6	(10–21)		33
7 (14–55)	0.5–1.8		13.8 (8.1–22.6)		12
3 (32–48)	3.1–4.7	3.9	17.0 (10–25.0)	Low corticoids	21
2 (18–65)	0.7–3.6	2.2			83
4 (adult)	1.0–4.3	2.5	14.7 (10.7–20.6)		118
9 (adult)		2.5	15.7 (10.9–20.5)		156
Women					
4 (adult)	1.7–3.6	2.5	8.7 (5.5–11.4)		118
7 (20–45)	0.5–1.4		9.0 (5.1–14.2)		12
2 (45–47)	1.7–5.1	3.4	11.0 (7.0–18.0)		21
1 (35)		1.6			83
3 (adult) postpartum		2.5	11.9 (4.3–19.5)		156
3 (39–41)	0.0–1.5	0.8	Ca. 12		152
3 (23–27)	1.3–3.8	2.2	(7–11)		194

TABLE 10

Excretion of Androgens and 17 Ketosteroids (Addison's Disease)

Number of Subjects (Age Range)	17 Ketosteroids: Range (mg. day)	17 Ketosteroids: Mean (mg. day)	17 Ketosteroids: Author's Mean Young Adult Value mg. day (Range)	Androgens: Range (I.U. day)	Androgens: Mean (I.U. day)	Androgens: Author's Mean Young Adult Value I.U./day (Range)	Ref
Men							
9 (1 34)	1 3-1 0	8 5	[illegible] 6 (1 9-34 0)				17
3				7 [illegible]	16 0		[illegible]5
3 (33- 8)	1 3 5	7	13 8 (8 1 [illegible] 6)				12
1 (28)		3 1	1 0 (10-2[illegible])				1
(adult)	0 9-8 8	3 8	14 (10 20 6)				118
6 (4-51)	1 -4 0		10 (4 9-18 4)				111
([illegible])				3-19	10 0	37 (1 104)	111
11 (18-51)	1 9-4 4	3 3					83
1 ([illegible])		7	15 (8 5-23 0)				120
2 (40-[illegible]0)	4 5- 1	5 8	1 6 (19 8-[illegible] 0)				1 9
36 ( )	1 0-8 0	4 2	15 0 (8 0-23 0)				149
Women							
5 (23-64		0	9 0 (1 14)				1
5 (adult)	1 4-10	5 1	8 (5-11 4)				118
5 (23-40)	0-8	5 4	16 (1 23)				119
(33-49)	1 0- 1	1 4	0 (1 5-9)				111
3 (29-56)	3 1 4 9	4	11 0 (0-18 0				1
4 (20-5)	0 6	1 0					83
5 (19-57)	1 5-3 6	9	8 4 (5 2 14 0)				120
4 ( )	1 3 0		8 2 (6 6-9 8)				1 9
3 (8-34)	1 1	1	[illegible] 11)				194
3 ( )	0 1 8 6	3 0	10 0 (5 0-12 0)				149
4 ( )				11 6	18		[illegible]5
(30-38)	1 3-4 4	3 1	12 6 (4 0-[illegible] 0)				1

One case was also eunuch.

Adrenocorticoid excretion has been reported normal or somewhat ele vated in the few cases studied [12, 21]

Pituitary basophilism will be discussed later in connection with adrenocortical hyperfunction

Thyroid disease

From the collected data in Table 13 it may be seen that a number of workers have encountered a depression of 17 ketosteroid excretion in the presence of hyperthyroidism The lowering however is only slight or moder ate Engstrom and Mason [11] analyzed their series for

TABLE 13

EXCRETION OF ANDROGEN AND 17 KETOSTEROIDS

(THYROID DISEASE)

Diagnosis	Sex	Number of Patients	Age	17 Ketosteroids: Mean mg/day (Range)	17 Ketosteroids: Author's Mean Normal Adult Level mg/day (Range)	Androgens (I U /day	Ref
Thyrotoxicosis	F	3	8-4	3 6 (1 3-5 6)	9 0 (1 14)		12
		1	32	6	11 0 (18)		21
		3	20-38	3 6 (3 0-4 8)	8 7 (1 12 6)		10
		17	16-60	5 1 (1 3-17 3)	8 2 (3 8-16 9)		19
		11	..5-67	7 2 (4 1 10 1)	10 2 (5 8-17 0)		11
			20 42	8 4 (7 3-9 6)	4 5 (3 8-4 8)	73 101	16
		22	21 9	10 6 (3 2 22 4) †	11 (5-20)		201
		5	1 -63	4 0 (3-5)	8 (6 5-10 0)		160
		4		(11)	9 (5-11)		118
	M	2	35 8	5 2 (5 1 5 3)	12 5 (6 7 27 2)		19
		2	..8-40	8 8 (6 4-10 7)	9 0 (3 5-15 0)	>44 .9	10
		11	4-65	10 4 (5 8-18 4)	14 2 (9 8-20 8)		11
		3	3 51	9 5 (6 7 12 8)	13 5 (8 4-19 2)	81 (9-103)	16
				0 9	15 (11 1)		118
Myxedema	F	7	35-67	1 8 (1 2 2)	10 (5 8-17 0)		11
		6	14-74	1 3 (0 8-1 8)	9 0 (5 1 14 2)		12
		1	..4	3 6	13 (8 4-19 2)	4	16
		2	11 15	1 8, 1 8	8 (6 5-10 0)		160
(Premenopausal)		9	17 47	2 4 (1 0-3 8)			207
Postmenopausal)		)3	41 7	2 3 (0 3-7 5)			207
		4	35-69	5 0 (4 3-6 0)	12 6 (4 0-22 0)		17
	M	2	?3-51	3 9 (1 8-6 0)	14 2 (9 8-20 8)		11
		6	36- 4	4 8 (2 5-8 7)			?07

Only 4 or 5 subjects in normal series.

† Mean postoperative values were 8 9 1 5 to days, and 10.6 1 3 to 4 months. Most of the goiters were of nodular type

The quantity of 17 ketosteroids in acromegaly appears to be highly variable In both sexes the values usually fall within the normal range but there are occasional assays which are either slightly above or below the limits of normal (Table 12) Failure to find a trend toward elevated values is somewhat surprising in view of the tendency toward adrenocortical hyperplasia and slight hirsutism in acromegaly

TABLE 12

EXCRETION OF 17 KETOSTEROIDS

(ACROMEGALY)

Number of Subjects (Age Range)	17 Ketosteroids			Ref
	Range (mg /day)	Mean (mg /day)	Author's Mean Normal Adult Level mg /day (Range)	
Men				
2 (28 39)	25 2–33 1	29 2	17 0 (10–25 0)	21
1 (31)		8 3	13 8 (8 1–22 6)	12
1 (53)		14 3	22 6 (15 9–34 0)	17
5 (adult)		23 4	14 7 (10 7–20 6)	118
1 (37)		6 0	(9–13)	194
Women				
9 (adult)		11 2	8 7 (5 5–11 4)	118
2 (26 30)	15 1–20 4	17 8		34
4 (28–43)	4 5–10 2	5 3	9 0 (5 1–14 2)	12
2 (32–54)	11 8–12 7	12 3	11 0 (7 0–18 0)	21
2 (28 50)	6 5–7 9	7 2	12 6 (4 0–22 0)	17
2 (23–46)	17 5–18 4	18 0	(7–11)	194

markedly lowered Inasmuch as the cases studied were considered to represent primary thyroid failure this effect has been interpreted as being due to a secondary depression of the adrenal The demonstration of little or no rise in 17 ketosteroid excretion after adequate therapy in many cases of primary myxedema[11,97] introduces the possibility of a superimposed pituitary deficiency due to irreversible damage suffered under the pre existing myxedematous state The degree of chronicity of the disorder thus may be important in relation to the reversibility of the depressed ketosteroid output

Testicular tumors

In cases of interstitial cell tumor with precocious virilization the excretion of 17 ketosteroids is distinctly elevated (Table 14) There are relatively few reports on the effect of teratomatous growths and seminomata Some values are slightly elevated but on the whole there is little deviation from normal Estrogen excretion is sometimes distinctly excessive and pregnanediol likewise may be elevated

Tumors and other lesions of the ovary and uterus

There is considerable uncertainty as to the origin nature and exact classification of masculinizing ovarian tumors Nevertheless no matter whether the tumor tissue resembles that of the adrenal corpus luteum or testis there is characteristically an increased production of androgen which is responsible for the virilism The effect of such tumors on 17 ketosteroid and androgen *excretion* is usually not as striking as one might anticipate (Table 15) There was no elevation in ten of twelve reported cases of arrhenoblastoma In two there was a distinct increase Five of eleven patients with lipoid cell tumors showed moderately elevated values but the others did not exceed the normal range That the *tumors actually produce androgen is testified by the* regression of virilization after resection It should also be noted that postoperative assays are generally lower than those before operation There is strong likelihood that masculinizing tumors of the ovary may produce a steroid which has high androgenic potency but which is not usually secreted in a sufficient amount to give rise to a large quantity of urinary metabolites The opposite is true with adrenocortical tumors The fact that the so called adrenal like tumors of the ovary are not consistently accompanied by an elevated 17 ketosteroid excretion suggests that the tumor cells are not physiologically similar to those of the usual tumor arising in the adrenal cortex From a clinical standpoint a low 17 ketosteroid assay in the presence of viri

any possible differences in excretion associated with the presence or absence of exophthalmos, diffuse hyperplasia or nodularity of the gland and were unable to demonstrate any modifying influence attributable to these variants The low values sometimes encountered in hyperthyroidism are most likely the result of a nonspecific reaction to chronic illness That thyrotoxicosis does not invariably lead to depressed excretion is attested by Kinnunen s finding of similar levels before and after thyroidectomy in a good sized group of patients [201]

Very low 17 ketosteroid values are encountered in myxedema It is thereby suggested that the capacity of the adrenal cortex and perhaps of the testis in male subjects to secrete 17 ketosteroid precursors is

TABLE 14

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(TESTICULAR TUMORS)

Type of Tumor	Age	Number of Patients	Clinical Manifestations	17 Ketosteroid (mg/day) Androgens (I U/day)	Other Assays	Ref
I t rst tial ll	41	1	Metastast	101 g		36
		1	Precoc ty	16 8 (1 0 po t-op)	0 β 17 k to t l	173
	3	1	Ir oc ty	64 mg (10 0 po t-op)	(I t j r al)	[illegible]
	2	1	Ir eoc ty	13 (0 post-op)	N g F d	18
	[illegible]	1	Pre oc ty	17 4 10 0 (3 8 post-op)		9
Se n		4		1 4 32 2 g		34
	39	1		80 I U	40 I U e t g	130
		1		30 I U	70 I U t gens	
	24	1		30 I U	30 I U est og n	
Ch n epith e-l oma	0	1	M t t s	27 g	4 g pregnaned l 30 I U e t e gonad t p 300 n se l t o g nits	
	3	1	M tastase	8 g	M re tl 2 000 M U g a lotrop	17
	3	2		13 1 nd 33 0 r g		34
T rat ma	[illegible]	1		16 8 g	68 I U estr ns g nadotr p 16 mouse t n t	17
		1		8 6 g		34
	4	1	M ta tases	0 I U	00 I U estrog ns	130
		1		30 I U	80 I U est g ns	

TABLE 15 (*Continued*)

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(TUMORS AND OTHER LESIONS OF THE OVARY AND UTERUS)

Diagnosis	Age	17 Ketosteroids (mg/day) Androgens (I U day)		Author Mean Normal and Range	Remarks	Ref
		Pre-op	Post-op			
Enlarged polycystic ovaries with hirsutism (sclerocystic ovaries, Stein-Leventhal syndrome)	13-3	37 I.U		47 (2 85) I U	Six cases. Menses variable Estrogens essentially normal.	9
	18- 7	17 24 mg			Three cases Estrogens (1 ?9 I U)	08
	?0	5 g		13 (4-)	Polycystic ovaries. Virilization. Adrenals normal to palpation	17
	?0	35 g			Polycystic ovaries Clitoris enlarged Amenorrh Aerogram of adrenals normal.	
		6- 1 mg Mean 13 mg.		9 (5-11)	F cases (t le ted)	118
	18	6 9 mg			Pregnanediol (19 7 mg)	1 4
	18	21 1 mg		(5 6-9 0)		180
	30	14 mg.				214
	3	3 8 mg.				215
	2 31	10 10 19 mg			Three cases	68
	6-30	2 6-12 9 mg. (Mean 7.5)			Six cases	69
Leydig cell (hilus cell) tumor	47	8 mg.				161
	46	0 mg.	11			203
	86	7 mg				66
	64	7 5 mg.				
Chorionepithelioma	22 31	4-10 mg			Three cases	1
Hydatidiform mole	6	7 3 mg				
	7	50 g			Pregnanediol corticoids d g ad tr p l ted	168
Granulosa cell tumor hirsutism adrenal hyperplasia	63	48 mg.		(4 0)	Estrogens (900 I U)	131

lism is against the diagnosis of adrenal tumor or hyperplasia A high value on the other hand does not exclude an ovarian tumor

In certain women who exhibit masculinizing stigmata sterility and amenorrhea the ovaries are found at laparotomy to be enlarged and polycystic (see Chapter 16) In twenty nine reported cases the 17 ketosteroid excretion was elevated *in only five instances* (Table 15)

TABLE 15

F xcretion oi Androgens and 17 Ketosteroids

(Tumors and Other I esions of the Ovary and Uterus)

Diagnosis	Age	1 K toste ds (g /day) Androgens (I U /d y)		A th Mea Normal d Rang	Remarks	Ref
		Pre-op	Post-op			
Ar he blastoma	30	g	4 mg	9 (5–14) mg		1
	4	4 mg	mg		Mathiese s ase	97
	8	60 I U			Wijse beek as	
	33	51 I U	10 I U		K te s case	
	16	1 I U	I U			99
	18	6 7 mg				60
	14	7 4 mg	6 3 mg			61
	6	46 0 mg	11 0 mg			26
	3	3 1 mg			Mal g t	63
	61	10 9 mg	8 8 mg			
	33	41 2 mg		13 (4–2) mg		1
	1	10 4 mg	9 3			16
I po d-c ll type (adr al pus l te m l k)	48	1 g 3 I U	6 mg	11 (4 ?) n g	Pre-op estr g ns (5 I U)	96
	50	14 mg 43 I U	3 u g 5 I U		Estr g mal	9
	16	55 mg	3 g		K pl r cas Virilism th aspe ts of Cushing y dr me Est og ns (190 I U)	
	3	16 I U			R tt o as Est og (33 I U)	
	44	4 mg			Estr g ns (37 I U)	8
	33	23 g	13 g		Ons t dur g p g y	104
	6	4 g 1 8 I U		13 (4– 2) r g	Estrog ns (00 I U)	105
	46	8 g	3 g		C ad tr p 0–40 m se u its	139
	15	1 ug	9 3 mg		Estr g (89 d 147 I U pre-op 15 I U post-op) Preg ned l (18 5 mg p e-op post-op)	140
	64	43 g	1 7 mg			64
	6	31 mg	5 6 r g		Pr g di l creased	65
	16	55 mg			F atur f Cush g y d m	244
	49	00 g			Cort c ds d ased adre al d p t tary tr phy	00
Dysge m ma	19	8 g	3 g	9 (5–14)	Mascul zat Othe ovary troph	1
	8	8 4 mg			F mal se precoc ty Pos Aschheim Zo d k	183

order In Table 17 the patients are described as having other aberrations such as hypertension obesity menstrual disorders or a distinctly prominent clitoris It should be pointed out that disease of the adrenal or ovary has not actually been ruled out by laparotomy in many of the reported cases of simple hirsutism

TABLE 17

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(HIRSUTISM WITH COMPLICATIONS * [ADULT WOMEN])

Number of Patients	Age Range	17 Ketosteroids		Androgens (I U /day)	Ref
		Mean mg/day (Range)	Author s Mean Normal Adult Levels mg /day (Range)		
2	20–29	16 (8–34)	12 6 (4–22) mg		17
13	20–38	7 8 (5–16)	3 4 (1 5–4 7) mg		65
10	Young adult		25 (20–40) I U	51 (30–92)	66
20	19–30	2 (4–37)			34
8	14–44	25 (10–100) †	6 4 mg		37
16	18–34	16 (9–32)	7 4 (3 5–14 6) mg	(36–82)	38
9	16–56			(30–300) ‡	27
9		13 (4–49)	9 5 (4–17) mg		24
26		(5–35)	6 4 (5–10) mg		35
13	18–59	24 (16–30)		(70–145)	58

* See text

† The patient who excreted 100 mg was shown to have normal ovaries and adrenals by laparotomy

‡ Capon units Normal range 10–50 C U /day

A series of cases from our own files which includes only patients with uncomplicated hirsutism shows a distribution of values illustrated in Fig 6 That the mean output for hirsute groups truly exceeds that of the controls is emphasized by the statistical significance of the difference Although anatomic disease of the adrenals and ovaries had not been excluded by exploration in most of the patients it is very unlikely that any great proportion suffered from such lesions

Pederson[10] encountered higher values for androgen excretion when there was an increased growth of hair over the linea alba (male

Simple hirsutism

Hirsutism in women is not always attended by anatomic lesions of the adrenal cortex or ovary In some instances a local factor within the hair follicle *may predispose to a relatively heavy growth in areas* such as the face abdomen and chest It is commonly believed that a

TABLE 16

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(SIMPLE HIRSUTISM)

Number of Patient	Age Range	17 Ketosteroids		Androgens (I U /day)	Ref
		Mean and Range	*Author s Normal* Adult Level mg /day (Range)		
17	17–37	19 (8–34)	12 6 (4–22)		17
11	20–36	16 (3 4–33)			34
5	18–31	14 (11–16)	7 4 (3 5–14 6)	33	38
2	21 29			27 37	93
4	16–54	28 5 (25–32)	11 (7–18)		91
15	17–34	8 (1 4–18)	3 4 (1 5–4 7)		65
12		12 (3–22)	9 5 (4–17)		94
138	15–68		14 (0–48) I U	21 (2–83) I U	100
3	27–43	5 1 ([illegible] 4–8 5)	8 4 (5 2–16 9)		107
8	21–41	10 1 (6 4–29 4)	8 5 (4 7–11 6)		164
3	20–40	27 (21–44)	5–8		192

Androgens by bioassay $t = 2\ 03$ $p = 0\ 05$

certain amount of circulating androgen is a *sine qua non* for the development of long coarse hair in these regions Perhaps therefore some women possess an unusual sensitivity to the normal levels of circulating androgen encountered in the female sex In other hirsute women the amount of androgen secreted within the body is undoubtedly higher than average Support for this thesis may be found in assays of 17 ketosteroids and androgens which have been reported In *most series* of cases of simple hirsutism the mean value for these urinary hormones has exceeded that of normal controls (Tables 16 and 17) The cases included in Table 16 are considered to be simple uncomplicated hirsutism without other evidence of any endocrine dis

TABLE 18

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS IN ADRENAL CORTICAL HYPERPLASIA *

Age	Sex	Remarks	17 Ketosteroids (mg day)	Ref
		F mal I d m Mal Sex I ecocity †		
3	F	Bilateral al nl g nt l y gra		
	F	Pse d h rm phrod t		
8	M	Sex precocity		
4	F	Pseud hermaphrodite	2	
10	F		13	12
3	F	Pse d h rmaphrodite	9	
5	F	Pseud hermaphrodite	4 d og ns	
1?	F	Pseud h rmaph odit	>50 C U	2
10	F	Pseud hermaphrodite	80-100 C U	
0	F	Pseud h maphrodite	13	
3	F	Virilism	37	40 1
27	F	Virilis		
18	F	Virilism	31	
		Prep be l nl t (4 f 7 cases nfed l y pe	0	
			3 4	6
Adult	F		3	
?13	F		35-64	
4 9	M	Prepuberal virilism (4 f b ases erified)	80-100 I U	38
11	F	Pre oc ou sex d elopm t (3 of 4 ases rified)	(1 g ns)	
		Onset ag 4 Est g ns 45 I U	47	
8 39	F		1 (17 31)	4
3	F	Pseud h aph od t	20 (8-33)	
		Bil teral nlarg m t l y ae gra Iseud h maphrodit	140 I U	
8	M		(drog ns)	48
	M	Onset precoc ty ge 4	34 102	
11	M	M d drenal disease	60	22
14	F	Onset b rtly fte b rth		13
	F	Pse d h maph odite	17	
	M	Se pre oc ty And g ns l ated Est og ns t d tect bl	1	
9 nths	F		9	
4	F	Pse d hern pl odite	11	
	F	Pseu d h rr ph odit	39	101
?	F	Pse d h rmaph odit		8
7	F	Pseud h rm phrod te	3	
3	F	Pse d h m ph odite	2	117
33	F	Pse d hermaph odite	8	197
5 8 16	F	Pse d h aph odite	12	
	I M	C g nit l (2 f 3 ase nfi d) C rt n no n l	14	
6	F		7	
	F	A d red (r c mpt hyperplas)	0	
17 41	F	Pse d h rmaph od t (est ds l t l)	8 00 28	
9 24	F	H rsutis		83
3	M	Pse d h m ph odit	80	
	F	Sex p ec ty Est g ns 100 300 I U	21	
8 18	F	Post t l hs	48 63 (a	107
11 1a wk	F	Pse d h aph odite (6 ases)	64 133	
4-7	M	Pseu d h rm ph rodit salt loss (3 ses)	6 8	131
		Se p ecoc ty (2 ases)	33	156
			44 30 6)	
			5 4 1	1 1
			8 6 6	

(Continued on next page)

escutcheon) In our own series this same tendency was noted Four cases out of the total of seventeen showed no hair over the linea alba. Their ketosteroid values were 8 12 17 and 19 mg This is a relatively low range when comparison is made with the average of 19 for the entire group

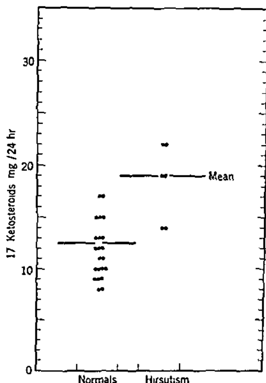


Fig 6 Excretion of 17 ketosteroids in simple hirsutism Most of the normal values represent the average of 3 24 hour samples The range of individual 24 hour assays is from 4 to 22 mg Difference between means = 6 4 ± St E of 1 72 P < 0 01

Adrenocortical hyperplasia

Hyperfunction of the adrenal cortex which accompanies adrenocortical hyperplasia may produce either virilization or Cushing s syndrome The former manifestation is the result of an increased secretion of androgen and is characterized by pseudohermaphroditism or adult virilism in the female and precocious pseudopuberty in the male Cushing s syndrome is characterized by a preponderant secretion of cortin like hormone rather than of androgen (Chapter 16) Values which have been reported in cases of adrenal hyperplasia are presented in Table 18 Assays must of course be interpreted in terms

of the age of the subject. A value of 13 mg at age 3 for example is distinctly high for this age.

As would be anticipated the 17 ketosteroid excretion tends to be markedly elevated in the virilizing type of disorder In Cushing's syndrome the values usually are slightly elevated but frequently do not exceed the normal range

Adrenocortical tumor

The clinical syndromes produced by functioning adrenocortical tumors resemble those associated with hyperplasia In the presence of a virilizing tumor 17 ketosteroid excretion frequently is even more dramatically elevated than in virilism due to hyperplasia (Table 19) Values above 100 mg a day are commonly seen Metastatic malignant tumors are sometimes responsible for an excretion which exceeds 1000 mg per day

In Cushing's syndrome there is a tendency for 17 ketosteroids to be somewhat low when a benign tumor is responsible for the disorder In contrast there is frequently but not always a massive output when the tumor is malignant This difference has been emphasized by Forbes and Albright [5] It would appear that although the physiological alteration in Cushing's syndrome is always dominated by an excessive secretion of 11 oxysteroids rather than potent androgens the quantity of the former may be so large in the presence of a malignant tumor that 17 ketosteroid metabolites accumulate in massive quantities (Table 19)

A functioning tumor in the adult male may lead to Cushing's syndrome or feminization but sometimes may not give evidence of any endocrine alteration The patient being already masculinized is not a suitable physiologic indicator for an increased output of the male type of hormone The 17 ketosteroid excretion is nevertheless frequently elevated no matter what the clinical manifestation might be

Cushing's syndrome without anatomic adrenal disease

In these cases the excretion is more often than not within the range of normal In the few instances of high output the values are only moderately elevated (Table 20) It should be pointed out that the separation of this category of cases from those with hyperplasia is undoubtedly artificial Hypersecretion exists whether or not hyperplasia can be demonstrated

TABLE 18 (*Continued*)

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS IN ADRENAL CORTICAL HYPERPLASIA *

Ag	Sc	Re arks	I ket te o d (mg /d y)	R f
		F male P t m Male S P ty †		
3–6	3 F 1 M	C ng n tal (3 c ses rfi d by operat n)	3 3 1 20	187
1 –16	F		69 8	118
Ad lt	F	P eudohermaphr dit m	21 152	
10 4	F	2 cases o e pl ed Pseudoh ermaph. Pregnane d l l ted	5 37	1 7
–4	F	P eudoher p l Adren l not e larged (4 ca es)	8 26 10	198
3 12	F	Pseud h m p l Ad enals enlarged (4 c ses)	19 15 43 43	
4	M	Se prec ty	16	
11 day – 21	2 F 3 M	Congenital (m xed ad en l di a e)	(3–18)	217
6	M	P ecoc ty w th sm ll t t Biop ed adrenal la ge but histol g lly normal	15	6
9	F	P d h pl	36 39	

		C h g S d m		
43	F		11	12
26	F		10	51
7	F		24	
9	M		8	
27	F	N l t g	20	43
20–38	1 M 3 F		(10–51)	83
13–47	2 M 6 F		18 (9–34)	0
6 39	F		7 6	34
7	M		31	23
13	2 M		16 8 18 8	23
11 14	F		(7 2 10 3)	
8	F		6	3
1 33	2 M		1 7 40 0	38
6–3	3 F		(4 4 13 4)	
[illegible]	F		21 0	23
[illegible]	F		1 4	240
	F	1F M	M 18 3	44
	M	5 ase	M n 8 3	
	F		1 6	17
0 9	M		16 8	0
9–38	F	3 ases	12 0 3	
4 30	F	Sl gt t bsy l a.	37 18	98
39	F	F t g 0 I U	16 5 (14 4 19 0)	1

* Hyperplas w s t blished eith by th g oss size of th gla ds mi osc p ppe e t operat n a topsy Presumpti ase are so nd t d n th table

† Alth gh me re not so d nt fied in the original repo ts most of these cases re do bt dly ong nital in origin.

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TABLE 19

Excretion of Androgens and 17 Ketosteroids in Adrenal Cortical Tumor

Age	Sex	Remarks	17 Ketosteroid (mg/day)	Ref
		*Female Virilism**		
26	F		63	37
41	F	Malignant	77	
	F	2 cases	36 126	4
5	F	Malignant nd og ns 321 I U	367	16
24	F	Hirsutism Adenoma	27	98
3 45	F	2 cases	110 8	51
13	F	Malignant Androgens 350 I U e t gens 310 I U	133	42
3	F	Malignant	160	
Adult	F	Malignant	74	
17	F	Adenoma Estrogen excret n no m l	Androgens 160 I U	49
2	F	Malignant (5 grams) Estrogens normal	78	52
3	F	Malignant	400	41
46	F	Malignant	518	17
	F	Malignant Est og n e creti n ncreased	Normal	
30	F	Malignant	2100	59
6 7	F	2 cases Estrogens ncreased	189 175	43
3 13	F	Malignant Second case had lements of C h ng s syndrome	160 166	13
16 36	F	Malignant E t gens n m l n first case	800 115 I U drog ns	29
14	F	Malignant (l g t m)	1980	10
3	F	Malignant Cortin excret n le ated	830	83
8 19 2	F	Adenoma Estrogens 330 to 1200 I U	60 111 2 8	131
10 5	F	Malignant m tastat F trog ns 200 to 12 000 I U	30 446	
27	F	Malignant	241	155
3	F	Malignant	00	158
28	F	Benign Est g ns 90 I U	7 0	162
28	F	Malignant? Hirsutism nly	2	165
4	F	Malignant Estrogens 45 I U	34	169
10	F	Malignant Som f at of C h g s y d om E t ge s 600 I U	826	18
3 35	F		41 74	186
1 2 19 57	F	Tumo	52 392 1,0	197
3	F	Malignant	67	
7 7	F	2 se Benign	16 173	198
7	F	Malignant	77	
1 63	I	3 es Malignant	6 75 6 0	118
		Male Sexual Precocity		
1 5	M	A d g ns 90 I U L se l	8 27	38
7	M	Malignant 1 kg n w g t	347	44
3	M	Malignant	34	17
7	M	Malignant Som a pe t f C h g s d m Estrogens 20 I U	141	98
5	M		378	186
6	M	Benign	189	198
6	M	Benign	19	166
		Adult M l M scell Effect		
39	M	D betes p ese t N th r ndoc in b ormalit es	5	51
3	M	No docr bn malit s	68	
34	M	Malignant F m niz t on Estrog ns 3000 I U /l	Androgens 0–100 I U /l	47
43	M	Malignant N ndocri al n rmal t Est o- g ns 300 I U	94	
34	M	Malignant F mi iz t E trog ns le ted	A d g s 80 C U /L	92
40	M	Malignant F minizati n	71	103
	M	Feminizat o Estrog ns l ted	-100 I U /L	
2	M	Malignant F m iz t	56	1 0

TABLE 19 (*Continued*)

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS IN ADRENAL CORTICAL TUMOR

Age	Sex	Remarks	17 Ketosteroids (mg./day)	Ref
		Cush g Synd m		
33 39	F	Ben gn ad n m ad n ma C t n ex ret n le- ated	9 6	21
36 36	F	M l gnant	74 0	1
7 34	F	Androg ns 800 I U /L case 1	1 0 2"0	38
6	M F	M l gna t Androg ns 145- 00 I U estrog ns 40-100 I U	49 497	3
61 38	F	I rst ase n t n d to be mal gna t	18, 3	37
34	F	Mal gnant	And g ns 300 C U	7
54 42 40	F	Malignant (3 ases)	83 090 126	34
63 5	F	(Predominantly C sl ng)	104 107 46	1
3 40	F	(P dominantly Cushi ng)	800 30	
66	F	M l gnant	74	42
31	F	M l gnant 660 g a s	5	
	I	M l gna t 1780 grams I reg anc t)) (I	15	4
6	M	M l gnant	44	2"0
6	F	Est g ns 188 000 I U	136	3
31 31	F	Est g ns n m l	A d g 13 141 U /L	9
6	F	B g t m	A d g 25 I U	93
7	M	M lignant	90	98
9	F	B nign	18	
33 4	F	C tis x ret n el ated	8 4	83
2	M	Mal gnant Est g ns 2 5 I U	1 7	131
	F	M l gnant	113	133
3 4	1 M 2 F	M lignant	4 6 1 0	155
4 24	F	M lign t	3 5	
50	F	A le m	6	
42	F	Malignant	4	18
30-37	F	7 ases B nign	(2 9)	0
36 51	F	2 ase Malignant	"0 1	
9	F	B nign aden ma	2 8	241
8	F	B gn d n a	6 9	235
18 42	F	B nign tum r	3 8 11 9	34
30	F	B gn tumo	6 1	38
2	F	B n gn tum	7 8	242
36	F	Be ign d n s	8 0	243
37	F	A drenal c nd last ase		
32 50	F	Ad m	2 6	44
1	F	Mal gnant	3 0	
1	F	Mal gn nt	1 1	
3	F	Mal gna t denoc n ma	849	
41	F	Ad nocarc n ma m l gn nt	45	
39	F	Adrenal car inom	6	24
42	F	M lignant Andr gens 500 I U /L	334	2"7 0

I ase mb ng f tures of both virilism nd Cushi ng ynd me n att mpt las been md t classify tl pat nts n the bas f th manifestat ns wh h d m n te the p t re

TABLE 19

Excretion of Androgens and 17 Ketosteroids in Adrenal Cortical Tumor

Age	Sex	Remarks	17 Ketosteroids (mg/day)	Ref
		Female Virilism		
6	F		63	37
41	F	Malignant	7	
	F	2 cases	36 1 6	4
5	F	Malignant androgens 3 1 I U	467	16
24	F	Hirsutism Adenoma	27	98
3 45	F	2 cases	110 - 8	51
13	F	Malignant And g ns 350 I U est gens 310 I U	133	4
3	F	Mal gnant	160	
Adult	F	M lignant	74	
17	F	Adenoma Est ogen excret n no m l	Androg ns 160 I U	49
2	F	Malignant (75 grams) Estrogens normal	78	2
3	F	M lignant	400	41
46	F	Mal gnant	516	17
5	F	Mal gnant Estrog n e cret on r creased	N rmal	55
30	F	Malignant	100	59
6 7	F	cases Est ogens ncreased	189 17	43
3 13	F	M lignant See nd case had leme ts of C hing s syndrom	160 166	13
16 6	F	Mal gnant Estrogens no m l n first case	600 115 I U a drogens	79
14	F	Malignant (large t m)	1980	107
3	F	Malignant Cort n e cret l ated	830	83
28 19 2	F	Adenoma Estrog ns 330 to 1 00 I U	60 111 2 8	131
10 5	F	Mal gna t metastatic Est g ns 00 to 1 000 I U	30 446	
27	F	Malignant	41	155
3	F	Maligna t	00	158
8	F	Benign Est og ns 90 I U	20	162
8	F	M lignant? Hirs tism nly	72	165
4	F	Mal gnant Est og ns 45 I U	34	169
10	F	M ligna t Some featu of C h ng s d om Est ogens 600 I U	8 6	18
3 35	F		41 74	186
1 2 19	F	Tum	5 2 392	197
57			120	
35	F	Maligna t	67	
7 7	F	2 ases Ben gn	16 1 3	198
7	F	Mal gnant	7	
1 63	1	3 ases Malignant	6 75 6 0	118
		Male Sex Precocity		
1 5	M	And g ns 90 I U L ase l	8 27	33
7	M	M ligna t 1 kg in w ght	34	44
3	M	M l gnant	34	17
7	M	M ligna t Some aspects f Cu h ng s dro Estrogens 0 I U	141	98
5	M		378	187
6	M	Be gn	155	198
6	M	Ben g	19	160
		Adult Male — Miscellaneous Effect		
33	M	D bet p esent N th ndocrin b ormalit es	5	1
3	M	N endoc bno mal t	68	
34	M	Mal gna t F m n t on Estr gens 3000 I U /l	A d g ns 50-100 I U /L	4
43	M	Maligna t N ndocr bnormalities Estrogens 300 I U	94	
34	M	Maligna t F miniz t n Est og ns l ted	A drog ns 80 I U /L	92
40	M	Malignant F minizat n	71	103
	M	F mini t Estrog ns l ted	100 I U /L	
	M	M l gna t F minizat o	8	1 0

TABLE 21

Excretion of Androgens and 17 Ketosteroids

(Precocious Sex Development—Miscellaneous Causes Excluding Clear Cut Adrenal or Testicular Disease)

Age	Sex	Remarks	17 Keto-steroids (mg/day)	R F
11	F	Fn or f al sex d l p t Obe ty Hy le y l ia	1 8	1
9	F	Sexual precoc ty Osteitis fil osa Skin pigment	1 4	
2	M	Testes dult Cause und term ned	9 6	1
4	M	Precoc ty with o t d m nstrable disease Estrog ns d g n d trop ns reased	3 5	31
11	M	P berty non bat ad need Estrog ns a d g nad trop ns n reased	16	
4	F	Breasts nd ut rus nlarged Estrogens nd gonad tr p ns in reased	9	
4	F	Breasts nla ged Estrog ns reased	3	
6	F	Breasts p b ha g l bleedi g Est g ns nd g n d trop ns n reased	7	
7	F	Breasts nla ged Estrog ns n reased	11	
7	F	Breasts a l bleedi g Estrog ns nd g na l trop ns n re sed	6	
11	F	P be ty lightly d nced Estrogens n reased	10	
4	M	S u pl somat nd se precoc ty		13
4	M	S m f dr f T tes la g f g C nsd red y l y re oc ty	9	101
	F	Breasts ginal bleeding	0 9	1
2	F	Bre ts ginal bleed ng o ria cy t	3	
3	F	Breasts ginal bleeding arian cysts	4	
4	F	Breasts ginal bleeding	1	
6	F	Breasts ag nal bleedi g	4 6	
9	F	Bre st ginal bleedi g	3 0	
11	F	Breasts ginal bleed ng	4 4	
2	F	R p d d l pment f ne breast	3 4	
6	F	Ra d d lopm nt f breast	4	
1	M	Phy l nd nt l p ecoc ty	1	
	M	Se l precoc ty	0	
6	M	Sex l p ecoc ty	6 0	
4	M	Il path mple precocious puberty	3	1
8 13	M F 1	I re oc g wth f p b h Quad pl gia	3 F	71
2 8	(1 M / 28 F)	P ecoc g th f sex h n k y l te p be ty	[illegible]	
2	F	H rto f tube	4	
7	M	N rofil atoma	1	
3	M	N d nstral l bra le n		

Mea l ra ge

TABLE 20

Excretion of Androgens and 17 Ketosteroids

(Cushing's Syndrome—No Adrenal Tumor or Hyperplasia*)

Age	Sex	R a k	17 Ketosteroids (mg/day) Androgens (I U/day)	R f
4	F	Ad e als g ssly n l at l pa t y H gl t e nt on	2 g	1
11	M	Adre al grossly n nal t l p ot y H gl t n exc t	11 ng	
49	F	Adrenal g sly n l at l par t ny	0 g	12
6	F	Adrenals gr ssly no mal at l p oto y	10 g	
1	F	N tum at laparotomy And gen 1 I U	15 g	3
33	F	Ad enals n r al at a t p y And g n 6 I U B gl lc a le noma (6 mm)		
8–43	F	No ad n l tumo F ur case l y t gla t r t l y r t ex cluded One case had r j t c	19 (7 29) mg	37
24	M	No anatom c abn mal ty of adren l Est g 1 I U	13 I U	48
23	F	No adrenal tun by air inj t	4 I U	
23	F	No dr nal tumo by air inj t	18 I U	
2	F	No dr nal t o by air j t n	30 I U	
4	M	Adrenals no mal by a r nj t n	27 I U	
37	F	E t ogens normal	25 I U	99
31 40	M	2 case Est ogens 11 to 23 I U	1 29 mg	98
16–38	F	se Ad nals normal by t p gl t j c t n Est g ns 5–39 I U	31 (10–45) mg	
17	F	B psy d	9 ng	200
11	M	No g oss bn rn lity	11 g	234
6 43	F	No tum On e pl d	11 15 ng	13

* Hyperpl a w n t l ded n ost se by d te m t n of weight r tudy of l st l g cal sect ns

Precocious sex development not associated with anatomic adrenal or testicular disease

There are occasional children of either sex whose sexual development is extremely precocious and yet in whom the gonads or adrenals are not the seat of any demonstrable lesion Such cases are sometimes physiologic variants although midbrain lesions may lead to precocity (Chapter 16) 17 Ketosteroid excretion is not extremely high Values are usually somewhat above levels that would be expected for the given age but do not exceed the adult range (Table 21)

Pregnancy

When 17 ketosteroids are determined by the dinitrobenzene reaction there is a steady increase as pregnancy progresses (Table 22) With the antimony trichloride reagent on the other hand no such rise is in

TABLE 23

EXCRETION OF 17 KETOSTEROIDS AND ANDROGENS

(SCHIZOPHRENIC MALES)

Type of Schizophrenia	Mean Age	No of Cases	17 Ketosteroids mg /day		Androgens I U /day		Ref
			Patients	Normals	Patients	Normal	
Paranoid	30	8	8.8	9.4 ± 0.6	31	43 ± 4	159
Simple	34	3	8.8		26		
Hebephrenic	34	7	9.4		33		
Unclassified	25	11	11.8		28		
Unclassified	3[illegible]	21	7.1 ± 0.[illegible] (11.4% β)	8.4 ± 0.3 (6.4% β)			190

± Standard error of mean

TABLE 24

EXCRETION OF 17 KETOSTEROIDS

(DIABETES MELLITUS)

Remarks	Sex	Age (years)	Number of Cases	17 Ketosteroids mg /day (Range)	Author's Mean Normal Adult Value mg / day (Range)	Ref
Diabetes	M	15–71	6	5 ([illegible]–7)	12 ([illegible]–27)	19
	F	[illegible]8–68	9	5 (2–7)	8 (4–17)	
Diabetics no insulin	M	21–58	10	8.9 (5–13)	15.0 (7–22)	1[illegible]9
	F	39–62	5	4.2 (3.2–5.1)	5.0 (4.7–7.5)	
Diabetics after insulin	M	21–58	7	11.1 (6.8–14.7)	5.0 (7–[illegible]2)	
	F	3[illegible]–62	3	5.4 (4.9–5.6)	5.[illegible] (4.[illegible]–7.5)	
Controlled	M & F	15–24	5	5.1 (4.2–6.2)		160

TABLE 22

EXCRETION OF ANDROGENS AND 17 KETOSTEROIDS

(PREGNANCY)

Age	Remarks	17 Ketosteroids * (mg /day)	17 Ketosteroids (2 weeks or more after delivery)	Ref
28	Normal pregnancy Repeated assays 1–10 months	11 (9–15)	8	12
32	Normal pregnancy 9 months	8	4	
28	Normal pregnancy 9 months	6	5	
22 to 35	6 normals 4 months	10 (5–15) SbCl$_3$ 10 (7–12)		91
	Same normals 8 months	23 (20–30) SbCl$_3$ 10 (10–12)		
	3 normals 6–8 months	Androgens 8 45 16 I U		9
	10 cases 2 months	6 5 (4 6–9 2)		175
	3 months	6 6 (5 4–8 2)		
	4 months	6 9 (4 6–9 9)		
	5 months	6 6 (5 0–8 0)		
	6 months	6 8 (4 8–8 6)		
	7 months	7 0 (5 6–10 3)		
	8 months	6 9 (5 0–7 5)		

* Dinitrobenzene reaction unless otherwise specified

evidence The few available determinations of androgens by bioassay likewise show no elevation The increase in 17 ketosteroid titer found with the dinitrobenzene reagent is due primarily to the color produced by pregnan 3 ol 20 one (XCIII) a nonandrogenic metabolite of progesterone (XCIV) Antimony trichloride does not give the characteristic color reaction with this steroid

Miscellaneous disorders

17 Ketosteroid excretion has been studied in a great variety of disorders some of which are listed in Tables 23 to 28 Psychotic patients

TABLE 23

EXCRETION OF 17 KETOSTEROIDS AND ANDROGENS

(SCHIZOPHRENIC MALES)

Type of Schizophrenia	Mean Age	No of Cases	17 Ketosteroids mg / day		Androgens I U / day		Ref
			Patients	Normal	Patients	Normals	
Paranoid	30	8	8 8	9 4 ± 0 6	31	43 ± 4	15[illegible]
Simple	34	[illegible]	8 8		26		
Hebephrenic	34	7	9 4		33		
Unclassified	25	11	11 8		28		
Unclassified	3[illegible]	21	7 1 ± 0 7 (11 4% β)	8 4 ± 0 8 (6 4% β)			100

± Standard error of mean

TABLE 24

EXCRETION OF 17 KETOSTEROIDS

(DIABETES MELLITUS)

Remarks	Sex	Age (years)	Number of Cases	17 Ketosteroids mg /day (Range)	17 Ketosteroids Author's Mean Normal Adult Value mg /day (Range)	Ref
Diabetes	M	1[illegible]-71	8	5 (2-7)	12 ([illegible]-27)	19
	F	[illegible]8-68	9	[illegible] (2-7)	8 (4-17)	
Diabetics no insul[illegible]	M	21-[illegible]8	10	8 9 ([illegible]-13)	1[illegible] 0 ([illegible]-22)	1[illegible]9
	F	39-62	5	4 2 (3 2-[illegible] 1)	[illegible] 6 (4 7-7 [illegible])	
Diabetics after insulin	M	[illegible]-58	7	11 1 (6 8-14 7)	5 0 (7-[illegible]2)	
	F	39-62	[illegible]	[illegible] 4 (4 9-[illegible] 6)	[illegible] (4 7-[illegible])	
Controlled	M & F	15-24	[illegible]	[illegible] 1 (4 2-[illegible] [illegible])		160

are within the range of normal (Table 23) whereas uncontrolled diabetics tend to give values somewhat lower than average (Table 24) as do patients with hepatic cirrhosis (Table 25) rheumatic disease (Table 26) anorexia nervosa (Table 27) hypertension malignancy, and paraplegia (Table 28) In almost all instances there is an

TABLE 25

EXCRETION OF 17 KETOSTEROIDS

(CIRRHOSIS OF LIVER AND HEPATITIS)

Remarks	Sex	Age (years)	Number of Cases	mg /day (Range)	Author s Mean Normal Adult Value mg /day (Range)	Ref
Cirrhosis	M	3[illegible]–60	6	1 5 (0 8–2 2)	11 5 (8–14 2)	160
	M	26–55	6	7 5	21 6 (19 8–25 0)	1 8
	M	19–60	14	7 2 (4 6–13 1)	12 (9 1–16 2)	2[illegible]3
	M	14–64	17	3 6 (0 7–8 8)	(10–20)	[illegible]74
Laennec s cirrhosis	M	57–64	6	7 6 (5 0–12 3)	9 0	163
	I	45–48	2	6 1–6 8	9 3	
Undetermined cirrhosis	F	19–50	5	7 0	9 4 (8 6–10 2)	
Biliary cirrhosis	I	46–50	3	7 6 (5 1–10 7)	8 7 (8 6–9 3)	
Portal cirrhosis			12	7 (1 5–13)	13 (7–22 5)	23
Chronic hepatitis			9	13 (10–19)		
Acute hepatitis			20	8 (2–24)		
Obstructive jaundice			5	6 (3–12)		

appreciable overlap with normal subjects In chronic debilitating disorders the tendency toward relatively low values is undoubtedly due to the nonspecific effect of long continued stress imposed by the disease

Table 29 is a summary of the alterations to be expected in various clinical conditions It should be emphasized that a statistical evaluation of published data is fraught with serious difficulties Not only are cases frequently reported in small numbers but a companion series of normal controls is often inadequate in size or completely lacking With the wide variability in normal values obtained with different analytical techniques it is impossible to establish a universal range of normal Estimates of deviation from normal in the table therefore are only rough tentative approximations

TABLE 28

EXCRETION OF 17 KETOSTEROIDS IN RHEUMATIC AND COLLAGEN DISEASES

Diagnosis	Sex	Age (years)	Number of Cases	17-Ketosteroids: mg/day (Range)	17-Ketosteroids: Author's Mean Normal Adult Value mg/day (Range)	Ref.
Ankylosing spondyl arthritis	M	25–41	11	27 (11–44)	14 (8–28)	[illegible]
	M	10–13	[illegible]	9.7 (3.6–1[illegible])	14 ([illegible]	[illegible]
	M		[illegible]	10.2 (8.4–13.2)	14 (8–23)	[illegible]
Chronic rheumatoid arthritis	F	[illegible]–52	11	13 (3–22)	10 (5–18)	[illegible]
	F	40–51	7	4.0 (2.7–5.8)	10 (4–11)	[illegible]
	F		36	8.6 (3[illegible]–21.8)	[illegible] ([illegible])	[illegible]
	F		17	3.5 (1–7)	9 (5–15)	18
	F	16–48	12	4 (1–8)	8 (4–1[illegible])	[illegible]
	M	20–66	7	7 (3–11)	12 (7–[illegible])	[illegible]
	M		26	6 (1.5–14)	11 ([illegible])	18
	M		31	12 (2.7–27.4)	14 (8–23)	[illegible]
Rheumatic fever	F	6–15	6	2.8 (1.5–4.8)		[illegible]
Scleroderma	F	28–35	2	8.2 (7.7–8.6)	10 (4–16)	[illegible]
Lupus erythematosus disseminatus	F	25–48	2	2.4 (1.2–3.6)	10 (4–16)	

TABLE 27

Excretion of 17 Ketosteroids

(Anorexia nervosa and Malnutrition)

Remarks	Sex	Age (years)	17 Ketosteroids: Number of Cases	17 Ketosteroids: mg./day (Range)	17 Ketosteroids: Author's Mean Normal Adult Value mg./day (Range)	Ref.
Anorexia nervosa	F	24–37	3	4 7 7	11 (7–18)	21
	F	20–31	6	4 (2–7)	9 (5–14)	12
	M		1	1 6	14 7 (10 7–20 6)	118
	F		11	6 6 (1 4–13 5)	8 7 (5 5–11 4)	
	F	17–30	5	8 (3–17)	13 (4–22)	17
Malnutrition	M	26–70	6	4 (2–8)	12 (7–27)	19
anorexia	F	15–44	27	5 (2–11)	8 (4–17)	
Anorexia nervosa	F	19–19	2	4 2	(7–11)	194

TABLE 28

Excretion of Androgens and 17-Ketosteroids

(Miscellaneous Disorders)

Diagnosis	Sex	Age (years)	Number of Cases	17-Ketosteroids mg./day (Range)	Normal Adult Mean mg./day (Range)	Ref.
Absence of gonadal tissue	M	2–36	3	7.5 (5.[illegible]–9.[illegible])	(1[illegible]–18)	114
Acne	M	Adult	9	Androgens 100 ([illegible]–1[illegible]6) I.U.	Androgens 87 (49–140) I.U.	109
	F		10	Androgens 7[illegible] ([illegible]–[illegible]) I.U.	Androgens 44 (30–94) I.U.	109
	F	Adults	8	1.8 ([illegible]2–[illegible]4) units	1.8 (0.5–3.8) units	143
Adiposogenital dystrophy. Gonadotropin assay low. Estrogens normal or slightly high	M	10–16	8	7 (4.5–16)	12 (7–19)	39
Adolescent [illegible]	M	12	6	8.8 (6.3–14.1)	11.[illegible]	124
	M	14	7	10.4 (7.7–19.[illegible])	13	
	M	1[illegible]	4	11.4 (8.0–14.[illegible])	13.[illegible]	
	M	16	3	13.1 (13.6–16.0)	15.9	
Benign hypertrophy of prostate	M	Old men	7	Androgens 7 (2–1[illegible]) I.U.	Androgens 9 (6–1[illegible]) I.U.	94
Myasthenia gravis	F	19–2[illegible]		4.3–8.5	9 (5–14)	12
[illegible]	M	[illegible]1–36	6	10.3 (8–[illegible])	10.2 (4.9–18.4)	111
Premenopausal cancer of breast	F	34–49	4	Androgens 30 (17–34) I.U.	Androgens 47 ([illegible]–8[illegible]) I.U.	1[illegible]6
Sp[illegible] dis[illegible]	M	18–31	3	2 (2–3)	12 (7–7[illegible])	19
	F	[illegible]0–[illegible]0	9	3 (0.5–8)	8 (4–17)	
Functional impotence	M	[illegible]0–[illegible]0	2	10 (1–[illegible]5)	14 (8–[illegible])	12
Gynecomastia associated with [illegible] in titer [illegible] 17-Ketosteroids [illegible] normal	M	0–4	13	10 (4–[illegible])	14 (3–[illegible]3)	22
Gynecomastia. Simple. Gonadotropins normal. No apparent endocrine abnormality	M	17–[illegible]0	7	14 (9–1[illegible])	[illegible]3 (16–34)	[illegible]7
Homosexuals	M	19–31	[illegible]	16.6 (10.1–27.7)	18.1 (11.2–30)	1[illegible]1
	M		3	14.6 (11.2–16.4)	14.[illegible] (10.7–20.6)	118
	F		2	13.2 (12.9–13.4)	8.7 (5.5–11.4)	
Hypertension	M	45–48	3	8 (3–13)	12 (7–[illegible]7)	19
	F	17–[illegible]0	8	3 (1–5)	8 ([illegible]4–1[illegible])	
	F	[illegible]8–70	40	8.4 ([illegible]–4.3[illegible])	14.2	9
	M	19–[illegible]	10	4.5 ([illegible]–5.8)	11.5 (8–14)	160
	F	[illegible]2–68	14	4.1 (2.[illegible]–14.0)	8.0 (6–10)	
Klinefelter's syndrome. Aspermia, high F.S.H., gynecomastia, small testes	M	17–38	8	8 (3.9–19.5)	13.3 (8.1–[illegible]2.[illegible])	1
Lead poisoning	M	[illegible]0–40	19	16.7 (10–31.[illegible])	2[illegible].6 (1[illegible].9–34.0)	123
Malignancy	M	[illegible]5–8	24	7 ([illegible]–[illegible])	12 (7–27)	[illegible]9
	F	1[illegible]–[illegible]0	5	3 (1–[illegible])	8 (4–[illegible])	
P[illegible]g	M	21–[illegible]6	36	17.1 (9.1–37.9)	21.6 (19.8–[illegible]0)	196
	F	21–68	16	7.3 (0–14.5)	(6–[illegible]1)	[illegible]6
Asthma	M		[illegible]	[illegible].8 (2.[illegible]–[illegible]1.5)	11.6 (7–1[illegible])	18[illegible]
	F		11	[illegible].0 (2–9)	9 (5–13)	
M[illegible] d[illegible]	M	3–17	3	[illegible] 1[illegible].6 4		198
	M	[illegible]4–[illegible]3	4	(5–7)		1[illegible]2
Leukemia	M	[illegible]8–67		4.2 (1.5–8.1)		141
	F	[illegible]0–74	[illegible]5	3.1 (0.9–[illegible].8)		
Poliomyelitis	M	14–39	[illegible]	14.4 (3.4–36.0)		142
	F	14–3[illegible]	13	8.0 (2.0–[illegible]1.1)		
C[illegible]t	M	[illegible]3–[illegible]9	10	3.2 (0.7–8.0)	(9–2[illegible])	210
	F	48	1	0.7	(7–1[illegible])	
Hermaphroditism		1	1	9		67
M[illegible]g[illegible]	M & F	[illegible]–6	14	(1–10)		66

TABLE 29

Excretion of Androgens and 17 Ketosteroids

(Summary)

Subjects and Clinical Condition	17 Ketosteroids and Androgens Compared to Normal Adult Level
Normal boys	
2–5 years	[illegible]
5–10 years	[illegible]
10–15 years	[illegible]
15–20 years	[illegible]
Normal girls	
2–5 years	[illegible]
5–10 years	[illegible]
10–15 years	[illegible]
15–20 years	[illegible]
Aged men	
50–60 years	[illegible]
60–70 years	[illegible]
70–80 years	[illegible]
80–90 years	
Aged women	
50–60 years	[illegible]
60–70 years	[illegible]
70–80 years	[illegible]
80–90 years	[illegible]
Eunuchoid men	Ketosteroids [illegible] Androgens [illegible]
Castrated men	Ketosteroids [illegible] Androgens [illegible]
Ovarian agenesis	Ketosteroids [illegible] Androgens Low (limited data)
Ovariectomy	Ketosteroids No change or increase; Androgens Possible decrease
Addison's disease	
Men	[illegible]
Women	
Panhypopituitarism	
Men	[illegible]
Women	[illegible]
Acromegaly	No constant deviation
Myxedema	[illegible]
Thyrotoxicosis	[illegible]
Interstitial cell tumor of testis	5- to 100-fold increase
Masculinizing ovarian lesions	Usually normal; occasionally 4 to 10 times normal
Simple hirsutism	Above average normal
Adrenal hyperplasia—Cushing's	About two times average normal
Adrenal hyperplasia—Pseudohermaphroditism or male precocity	About 10 times normal
Cushing's—no definite adrenal tumor or hyperplasia	Ketosteroids less than twice average normal. Androgens Slight decrease (?)
Adrenal cancer—Cushing's	About 2 to 100 times [illegible] normal
Adrenal tumor—Cushing's not malignant	One-third to two times normal
Adrenal cancer—virilism	10 to 100 times normal
Adrenal tumor—virilism not malignant	[illegible]-fold increase
Human pregnancy (diastrobe [illegible] agent)	
4th month	No change
8th month	About two times normal
Metastatic malignancy (not adrenal or gonadal)	About one-half normal
Malnutrition and anorexia nervosa	[illegible] to [illegible]
Diabetes uncontrolled	About [illegible]
Cirrhosis of liver	[illegible]
Hypertension	About half normal
Rheumatic and collagen disease	Slight to moderate reduction
Homosexualism	No established difference from normal

Androgens and 17 Ketosteroids in Blood

The most extensive study of androgen concentration in human blood is Tornblom's[134] Previously Womack and Koch[135] had obtained growth of the capon's comb with extracts equivalent to 300 to 600 ml of bull's blood McCullagh and Osborn[16] reported that the blood of normal young men contained 4 I U of androgens per 100 ml

Tornblom subjected human blood to sulfuric acid hydrolysis followed by the addition of sodium sulfate and the extraction of androgens with benzene The neutral fraction was assayed in terms of testosterone by direct application to the capon's comb Table 30 summarizes the findings Normal men between the ages of 20 to 29 years

TABLE 30

ANDROGENS IN HUMAN BLOOD

(Tornblom [illegible])

Status of Subject	Age (years)	Number of Subjects	Androgens in Blood (µg testosterone/100 ml ± S E) (Range)
Normal men	[illegible]	3	4 69 ± 0 [illegible]
	30-4[illegible]	18	2 [illegible] ± 0 6
	46-[illegible]	13	1 [illegible]6 ± 0 34
N[illegible]	0-36	10	7 5 ± 3 5 (0 4 33 8)
Castrated	0-61	8	0 68 ± 0 18
O[illegible]ectomized w[illegible]	8-4[illegible]	7	1 1 ± 0 5 (0-3 2)
P[illegible] hypertrophy	60-75		1 96 ± 0 31
[illegible]	0		1 3
[illegible] type	4		8 3
H[illegible] adrenals [illegible]	25		9 8
H[illegible]—hypertrophy [illegible] of adrenals			1 4
H[illegible]	8		1 0
H[illegible]—ovary [illegible]	[illegible]		11
H[illegible]—adrenals [illegible] regul[illegible]	31		0 7
Ad[illegible] H[illegible]	31		[illegible]
Hypert[illegible]	[illegible]7		4
H[illegible]—ova[illegible]	7		0
H[illegible]—adren[illegible]	30		0 8

had concentrations of 4 69 ± 0 59 µg per 100 ml of blood Significantly decreased amounts of androgens were found with increasing age after 30 The mean value for women was 7 5 ± 3 5 µg testosterone but the variation among individuals was extremely great (0 4 to 33 8 µg) Both castrated men and ovariectomized women had low

values No significant deviation from normal was apparent in a small series of hirsute women

Various methods have been suggested for the determination of 17 ketosteroids in peripheral blood[247-49] Of these Gardner s method[246 249] though not extensively studied seems promising Six to 10 ml of plasma from oxalated or heparinized venous blood is hydrolyzed with 10 per cent hydrochloric acid and the hydrolyzate extracted with ether After chromatography on magnesia silica gel columns the proper residues are subjected to micro Zimmermann reactions Spectrophotometric curves of the Zimmermann reaction show a convincing peak at 520 mμ and an unexplained maximum at 405 mμ By use of this method a range of 40 to 130 μg of neutral 17 ketosteroids per 100 ml of plasma was obtained in adult men and 25 to 100 μg in adult women Four children aged 6 to 13 years suffering from congenital adrenal hyperplasia had values ranging from 80 to 360 μg per 100 ml of plasma Low or undetectable values were obtained in normal children 3 to 5 years of age

β 17 Ketosteroids

The β 17 ketosteroids or more specifically 3 hydroxy β 17 keto steroids are those stereoisomers in which the hydroxyl group at position 3 of the molecule is on the same side (*cis*) of the ring as the methyl group at position 11 (see Chapter 4) The known β 17 keto steroids of urine are dehydroepiandrosterone which is the principal component (XXIII) and epiandrosterone (XXI) the minor component Since the β fraction is generally high in adrenal cancer an assay for β 17 ketosteroids is of diagnostic importance

Chemically the β 17 ketosteroids are precipitable as a group by treatment of the urinary extract with digitonin This procedure requires a fairly careful and standardized chemical technique in order to obtain reproducible results In the absence of any one uniform procedure to be followed by all laboratories it is not surprising that variations of considerable magnitude may be encountered The method of hydrolysis and extraction of the urine also has a decided effect on the content of β ketosteroids Thus dehydroepiandrosterone (XXIII) may undergo conversion to $\Delta^{3\ 5}$ androstadien 17 one (LIII) or 3 chloro Δ^5 androsten 17 one (XXIV) or both during acid hydrolysis If extraction is carried out with heat at neutral *p*H the principal artifact is i androstan 6β ol 17 one (XL) These artifacts are not β 17 ketosteroids do not precipitate with digitonin and the resulting assay values for the β fraction are thus erroneously low (Chapter 5)

The summary of the literature given in the following sections must be taken as an indication of a trend rather than a measure of absolute values For clinical application of the digitonin fractionation it is almost mandatory that a laboratory establish its own series of normal values

Normal subjects

Table 31 summarizes the β 17 ketosteroid values which have been reported in normal subjects Values range from zero to 18 per cent

TABLE 31

β 17 KETOSTEROIDS IN THE URINE OF NORMAL INDIVIDUALS

Age (years)	Sex	17 Ketosteroids (mg /day)	β 17 Ketosteroids (% of total)	References
4-7	M + F pool	1 3	8	13
7-12	M + F pool	4 0	8	13
12 15	M + F pool	8 5	5	15
15+	F pooled	10 2	11	13
17	F	16 2	5	233
35	F	14 9	3	233
	4-7 months pregnant	15 1	13	13
33	Pregnant	4 5	2	233
15+	Pool M	15 0	8	15
21	M	16 7	6	233
35	M	26 1	5	233
Adult	M	13 9	0	224
Adult	M	16 0	18	224
20-35	Pool M	18	1	219
16 38	M + F	14 (Av of 6 cases)	0 6 to 2 2	22
22-3	9 months pregnant	20 (6 cases)	8 *	91
20- 9	M	15 9	15 (2 to 33)	149
22 54	F	9	18 (0 to 57)	

* No change in absolute level throughout pregnancy

and there appears to be no difference between the adult and the pre puberal child males and females or the pregnant and nonpregnant state In all instances the β 17 ketosteroid excretion is reported to amount to less than one fifth of the total and averages one tenth to one-twentieth

Recently Bitman and Cohen [22] have compared the yield of β keto steroids obtained after classical acid hydrolysis with the quantity re covered after milder treatment After employment of the latter proce dure the β fraction of a pooled sample of normal urine comprised 13

per cent of the total as contrasted with 4.5 per cent after routine hydrolysis This suggests that values heretofore reported are too low

Adrenocortical tumor

The one condition which is usually associated with a striking alteration in the β fraction is adrenocortical tumor (Table 32) It is of

TABLE 32

β 17 KETOSTEROIDS IN ADRENAL CORTICAL TUMORS

Age	Sex	Total 17 keto (mg /day)	β 17 keto % of Total	Remarks	References
7	M	40	42	Malignant sexual and somatic precocity	44 6
42	F	367	19	Malignant N[illegible]	7
3	M	68	48	No endocrine abnormalities	0
25	F	107	60	Predominantly Cushing's syndrome	
40	F	30	8	Predominantly Cushing's syndrome	
3	F	800	69	Predominantly Cushing's syndrome [illegible]	
	F	100	77	Clinical type not specified Metastat[illegible]	
43	M	94	3	No endocrine abnormalities Malignant	8
	F	9	9	Virilism Malignant	
31	F	7	74	Obesity Hypertrichosis Malignant	
	F	1 1	64	No clinical description Malignant	4
19	F	12	38	No description of [illegible]	[illegible]
28	F	42	6	No description of case	
6	F	1 0	28	Cushing's syndrome Malignant	9
3	F	160	6	Virilism Malignant	13
13	F	166	50	Virilism with [illegible] of Cushing's syndrome Malignant	
8	F	2100	35	Malignant Virilism	219
25	F	80	32	Malignant Virilism	
6	F	74		Cushing's syndrome Malignant	4
Adult	F	74	38	Virilism Cancer	
4	F	0	0	Virilism Adrenal [illegible]	219
6	M	19		Pre[illegible] Adrenal benign	
6	F	136	1	Cushing's syndrome Malignant	40
1	F	8	66	Virilism Malignant	10
8	F			Hirsutism [illegible] Malignant	16

*[illegible] dehydroiso[illegible] isolated

course in such cases that extremely high values for the total 17 ketosteroid excretion are encountered The elevation is due in large part to the presence of excessive amounts of β compounds such as dehydroepiandrosterone (XXIII) The magnitude of the β fraction varies from zero to 79 per cent and averages 45 per cent Of the twenty five cases which are tabulated only four are definitely in the range of normal (less than 20 per cent) Two of these who were children studied in our own laboratory [1] had a benign tumor A third was a case of Cushing's syndrome reported by Kepler and Mason [illegible] Most of the cases listed in the table were suffering from a malignant

type of tumor but in many instances no statement as to the nature of the tumor has been included in the original case report Conclusions therefore cannot at present be drawn concerning the relation of malignancy and benignancy to the excretory level of this fraction The data to date do not disclose any difference in excretion between the tumors associated with virilism and those which result in Cushing's syndrome

Adrenal hyperplasia

The clinical manifestations of adrenocortical hyperplasia are often identical with those of tumor and the total 17 ketosteroid excretion likewise is substantially elevated in virilism due to either lesion The β 17 ketosteroids on the other hand are either normal or only slightly elevated in cases of hyperplasia (Table 33) The range in the twenty nine listed cases is from zero to 24 per cent and there is only one

TABLE 33

β KETOSTEROIDS IN ADRENAL CORTICAL HYPERPLASIA

Age	Sex	Total 17 Ketosteroids (mg/day)	β Fraction (% of total)	Remarks	Reference
10	F	31	14	[illegible]	0
23	F	13	0	[illegible]nal pseud[illegible] adults	
7	F	24	14	Cushing's syndrome	
9	M	8		Cushing's syndrome	
2?	F	10	5	Cushing's syndrome	
27	F		7	No description of case	3
8	F	66		No description of case	
8	M	17	4	Sexual precocity	13
7	F	60	2	Virilism	[illegible]
0	F	87	0.3	Virilism	
28	F	36		Virilism	
13	M	6	4	Precocious sexual development [illegible]	
	M	4		Precocious sexual development [illegible] hyperplasia	
2	M	1	7	Precocious sexual development [illegible]	13
4	M	8	10	Precocious sexual development [illegible] hyperplasia	4
	M	0	0	Precocious sexual development [illegible]	
8	M	33		Precocious sexual development [illegible]	
5	F	19	18	Virilism	
6	F	17	0	Virilism [illegible] hyperplasia	
7	F	31	6	Virilism [illegible] hyperplasia	
8	F	1	0	Virilism	
9	F	2		Virilism [illegible] hyperplasia	
11	F	3	0	Virilism	
13	F	3	3	Virilism	
3	F	72	9	Virilism [illegible] hyperplasia	
4	M	18	6	Precocious development [illegible] hyperplasia	
Adult	F	47	14	Virilism	
7 27	M & F	3-60	4 11	Four cases [illegible]	
0	M	2	7	Precocity	143

instance of a value in excess of 20 per cent The over all mean is 9 per cent which is essentially identical with that of the normal series Thus it is evident that an assay of this fraction may be of distinct help to the clinician in the differentiation of adrenocortical tumor from hyperplasia

Miscellaneous conditions

The data compiled in Table 34 show no clear indication of a deviation from normal in the various disorders which are listed Callow

TABLE 34

β KETOSTEROIDS IN MISCELLANEOUS CONDITIONS

Ag	Se	T t l 17 Keto (g/da)	β K ct o (f t tal)	Re a k	R f e
4	M		23	S pl pre ty I batly n adrenal d sease	13
43	I	1	7	Cush g s yndro N t r	13
6	1	11	1	Cu h g s ynd me N to	13
0	1	5	3	I lycyst c o n s Adre als n r mal to p lpat o Pseudo-h rmapl oditism	219
33 62	I	6 6	2 8	C n r of b ea t	3
60 6	M	4 3	0 4	C n r of p ostate	
56 80	M	7 (4 10)	7 (1 11)	Can r of prostate β K a t n afte trat o 5(-11)% 8 se	90
14 63	M & F	8	0 3 t 6	C r p t nt	
0	F	35		I oly y t o	19
6	F	74	1	M sc l g d e l t o of ry	10
45	M	4	0	I l f 3 a es L ren e Moo B edl ynd	219
2	M	6	9	Addis n d se	149
23 40	F	1 4 4 6	1	Addison d sease	
21 5	M	13 7 5	10 0	E nu l d n	

and Callow [30] obtained a higher proportion of dehydroepiandrosterone (XXIII) in the urine of a eunuch than in pooled normal male urine

Summary of β 17 ketosteroid excretion

The β 17 ketosteroids normally constitute less than 20 per cent of the total neutral 17 ketosteroid fraction and there are no demonstrable deviations due to age sex or pregnancy The only clinical disorder which is associated with abnormal values is adrenocortical tumor which usually but not always is accompanied by a substantial rise

Individual 17 Ketosteroids of Urinary Extracts

A limited number of human urinary extracts have been studied by the method of Rubin et al [1] for the quantitation of individual 17 keto

TABLE 3ɔ

α 17 Ketosteroids in Human Urine

(Data of Rubin et al [a] and Dorfman [b])

Type of Subject (age range in years)	Number of Subjects	Mean ± S E (mg /day)						
		Total α 17 keto-steroids	Androsterone	Etiocholan 3α-ol 17-one	Androstane-3α 11β-diol 17-one	Etiocholane-3α 11β-diol 17-one	Androstan 3α-ol 11 17 dione	Etiocholan 3α-ol 11 17 dione
Normal men (19–3ɔ)	8	12 0 ± 1 9	3 36 ± 0 ɔ7	3 89 ± 0 ɔ9	0 73 ± 0 13	0 3ɔ ± 0 11	0 3ɔ ± 0 06	0 ɔ1 ± 0 07
Normal men (0–88)	4	2 6 ± 0 10	0 6 ± 0 10	0 03 ± 0 08	0 24 ± 0 03	0 22 ± 0 04	0 08 ± 0 01	0 19 ± 0 02
Normal women (21–3ɔ)	6	10 4 ± 1 8	3 80 ± 0 ɔ9	3 0ɔ ± 0 ɔ6	0 78 ± 0 19	0 29 ± 0 0	0 21 ± 0 03	0 4ɔ ± 0 12
Normal women (74–78)	3	4 1 ± 0 3	0 83 ± 0 16	1 42 ± 0 07	0 49 ± 0 12	0 18 ± 0 04	0 10 ± 0 01	0 ɔ6 ± 0 07
Adrenal cancer Viri lism (4 5) 1 M 3 F	4	22 2 ± 9 0	7 67 ± 3 2ɔ	4 ɔ2 ± 1 70	1 0 ± 0 6ɔ	0 76 ± 0 50	0 ɔ6 ± 0 38	1 08 ± 0 70
Congenital adrenal hyperpla ia (3–16) 2 M 2 F	4	42 ɔ ± 8 0	9 24 ± 1 0	ɔ 76 ± 1 20	8 40 ± 2 0	2 17 ± 0 34	2 21 ± 0 ɔ9	2 28 ± 0 ɔ0

steroids These values are presented as an example of an analytical method which shows promise for the study of steroid metabolism in health and disease This approach coupled with a growing knowledge of steroid interconversion and degradation will lead the way to a better understanding of the functional status of those organs which produce the steroid hormones

In normal adult men and women androsterone (XXV) and etiocholan 3α ol 17 one (XXII) are present in the highest concentration and in a ratio of approximately 1 1 (Table 35) These metabolites arise primarily from Δ^4 androstene 3 17 dione (LXI) and dehydroepiandrosterone (XXIII) derived from the adrenal cortex in both men and women and from testosterone (VIII) derived from the testis in men 17 Hydroxyprogesterone (LIX) and 17 hydroxy 11 desoxycorticosterone (CXVII) of the adrenal cortex contribute a minor portion of etiocholan 3α ol 17 one (XXII) and a still smaller amount of androsterone (XXV) to the urine [204]

The 11 oxygenated 17 ketosteroids derived from adrenal compounds are present in a lower concentration than is true for the 11 desoxy 17 ketosteroids Approximately 2 mg per day are excreted in both men and women of the lower age group Those of the etiocholane series are probably contributed mainly by hydrocortisone (CXV) and those of the androstane type mainly by adrenosterone (LX) and Δ^4 androsten 11β ol-3 17 dione (CXXIV) [204]

The patients with adrenal cancer have only a modest increase in 11 oxygenated 17 ketosteroids whereas those with hyperplasia show a sharp increment in these compounds particularly the 11 oxygenated derivatives of the androstane type which arise primarily from adrenosterone (LX) or Δ^4 androsten 11β ol 3 17 dione (CXXIV)

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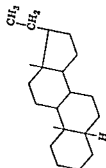
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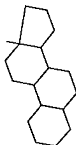
APPENDIX A

Names and Structural Formulae of Compounds

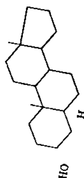
Compound Number	Structure	Systematic Name (Common Name)
I	H	Androstane
II	H	Etiocholane
III	CH_3 CH_2 H	Allopregnane



I regnane



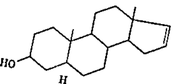
I strane



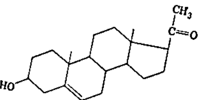
An dro tan-3α-ol

Compound Number	Structure	Systematic Name (Common Name)
VII	HO, H	Androstan 3β-ol
VIII	O, OH	Δ^4 Androsten 17β-ol 3-one (testosterone)
IX	HO, H	Δ^{16} Androsten 3α-ol

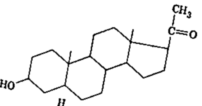
XII



Δ^{16}-Androsten-3β-ol



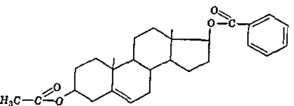
Δ^{5}-Pregnen-3β-ol-20-one (Pregnenolone)



Allopregnan-3β-ol-20-one

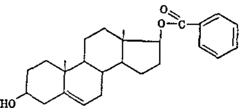
Compound Number	Structure	Systematic Name (Common Name)
XIII		Cholesterol
XIV		Δ^5 Androsten 3β ol 17-one-3-acetate (dehydroepiandrosterone acetate)
XV		Δ^5 Androstene 3β 17β diol 3-acetate

XVI



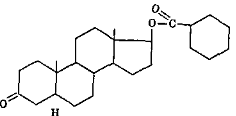
Δ^5 Androstene-3β 17β-diol 3-acetate 17 benzoate

XVII



Δ^5 Androstene-3β 17β diol 17 benzoate

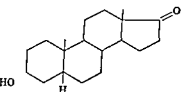
XVIII



Androstan 17β-ol 3-one 17 hexahydrobenzoate

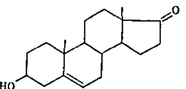
Compound Number	Structure	Systematic Name (Common Name)
XIX	OH, C≡CH, O	17-Ethynyl-Δ^4-androsten-17β-ol-3-one (ethynyltestosterone)
XX	OH, CH_3, HO, H	17-Methylandrostane-3β,17β-diol
XXI	O, HO, H	Androstan-3β-ol-17-one (epiandrosterone, old common name isoandrosterone)

XXII



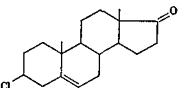
Etiocholan-3α-ol-17-one (etiocholanolone)

XXIII

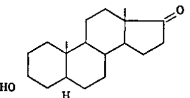
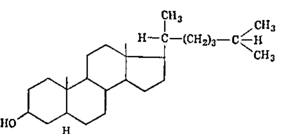
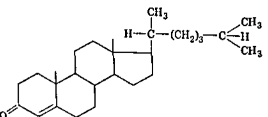


Δ^5-Androsten-3β-ol-17-one (dehydroepiandrosterone; old common names: dehydroisoandrosterone, transdehydroandrosterone, dehydroandrosterone)

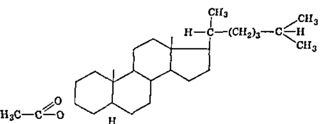
XXIV



3β-Chloro-Δ^5-androsten-17-one

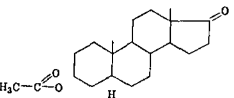
Compound Number	Structure	Systematic Name (Common Name)
XXX		Androstane 3α ol 17 one (androsterone)
XXXI		Dihydrocholesterol
XXXII		Cholestenone

XXVIII



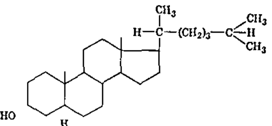
Dihydrocholesterol acetate

XXIX



Androstan-3α-ol-17-one acetate (androsterone acetate)

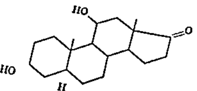
XXX



Epidihydrocholesterol

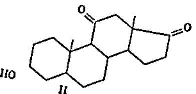
Compound Number	Structure	Systematic Name (Common Name)
XXXI	$H-C(CH_3)-(CH_2)_3-C(H)(CH_3)_2$; HO; H	Coprosterol
XXXII	$H-C(CH_3)-(CH_2)_3-C(H)(CH_3)_2$; HO; H	Epicoprosterol
XXXIII	O; HO; H	Etiocholan-3β-ol-17-one

XXXIV



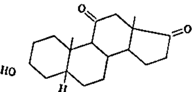
Androstane-3α,11β-diol-17-one (11β-hydroxyandrosterone)

XXXV



Androstan-3α-ol-11,17-dione (11-ketoandrosterone)

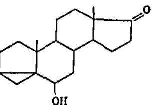
XXXVI



Etiocholan-3α-ol-11,17-dione (11-ketoetiocholanolone)

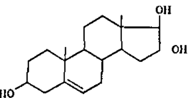
Compound Number	Structure	Systematic Name (Common Name)
XXXVII		Etiocholane 3α 11β-diol 17-one (11β hydroxyetiocholanolone)
XXXVIII		Androstane-3 11 17 trione
XXXIX		Androstane 3α 17β-diol

XL



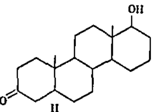
i Androstan 6β-ol 17-one

XLI



Δ^5 Androstene-3β 16α 17β triol

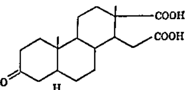
XLII



D Homoandrostan 17a-ol 3-one

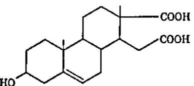
Compound Number	Structure	Systematic Name (Common Name)
XLIII	CH_3, C=O, OH, HO	Δ^5 Pregnene-3β 17α-diol 20-one
XLIV	OH, OH, HO	Estriol
XLV	O, HO	Estrone

XLVI



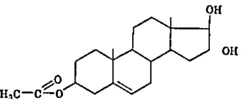
3-Ketoetioallobilianic acid

XLVII



β 3-Hydroxy Δ^5-etiobilienic acid

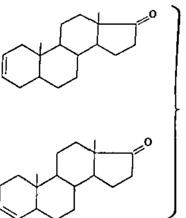
XLVIII



Δ^5 Androstene-3β 16α 17β triol 3-monoacetate

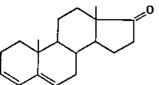
Compound Number	Structure	Systematic Name (Common Name)
XLIX	HO, OH	Δ^5 Androstene-3β 17β-diol
L	HO, OH	Estradiol 17β (old name α-estradiol)
LI	HO, H_3C, OH, =O	17a Methyl Δ^5 D-homoandrostene 3β 17a(α)-diol 17-one

LII



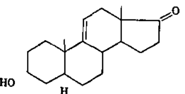
Δ^{3} Androsten 17-one

LIII



$\Delta^{3,5}$ Androstadien 17-one

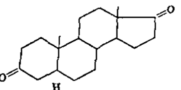
LIV



$\Delta^{9(11)}$ Androsten-3α-ol 17-one

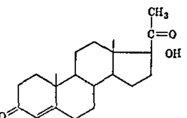
Compound Number	Structure	Systematic Name (Common Name)
LV		$\Delta^{9(11)}$ Etiocholen *3α-ol 17 one*
LVI		3α Chloroandrostan 17-one
LVII		Tetradecahydro-1 7-diketo-2 13-dimethylphenanthrene

LVIII



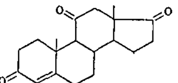
Andro tane-3 17-d one

LIX



Δ^4 I regnen 17α-ol-3 20-dione (17α hydroxy progesterone 17 hydroxyprogesterone)

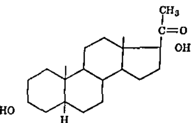
LX



Δ^4 Androstene-3 11 17 trione (a lrenosterone)

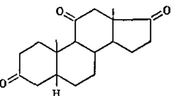
Compound Number	Structure	Systematic Name (Common Name)
LXI	O, O	Δ^4 Androstene-3 17-dione
LXII	HO, O, HO, H	Androstane 3β 11β diol 17-one
LXIII	CH_3, H—C—OH, OH, HO, H	Pregnane 3α 17α 20α triol

LXIV



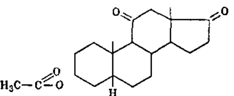
Pregnane-3α 17α-diol 20-one

LXV



Etiocholane-3 11 17 trione

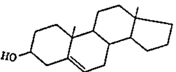
LXVI



Etiocholan 3α-ol 11 17-dione acetate

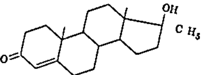
Compound Number	Structure	Systematic Name (Common Name)
LXVII		Androstan 17-one
LXVIII		Δ^5 Androstene
LXIX		Δ^{11} Androsten 3α ol 17-one

LXX



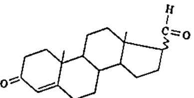
Δ^5 Androsten-3β-ol

LXXI

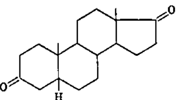
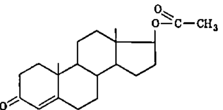
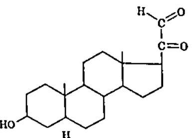


17 Ethyl Δ^4-androsten 17β-ol 3-one (17-ethyltestosterone)

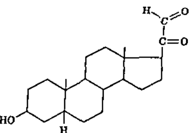
LXXII



17 Formyl Δ^4-androsten-3-one

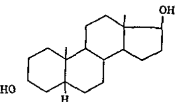
Compound Number	Structure	Systematic Name (Common Name)
LXXIII		Etiocholane 3 17-dione
LXXIV		Δ^4 Androsten 17β ol 3-one acetate (testosterone acetate)
LXXV		Allopregnan 3β-ol 20-on 21-al

LXXVI



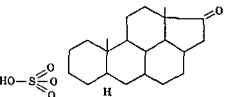
Pregn n-3β-ol 20-on 21 al

LXXVII



Etiocholane-3α,17β-diol

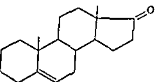
LXXVIII



Androstan 3α-ol 17-one sulfate (androsterone sulfate)

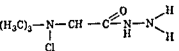
Compound Number	Structure	Systematic Name (Common Name)
LXXIX		Androstan 3α-ol 17-one glucuronide (androsterone glucuronide)
LXXX		Δ^5 Androsten 3β-ol 17-one sulfate (dehydroepiandrosterone sulfate)
LXXXI		Δ^5 Androsten 3β-ol 17-one benzoate (dehydroepiandrosterone benzoate)

LXXXII



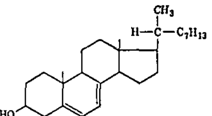
Δ^5 Androsten 17-one

LXXXIII



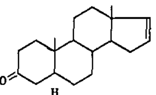
Trimethylacethydrazide ammonium chloride (Girard's Reagent T)

LXXXIV

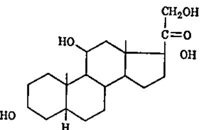
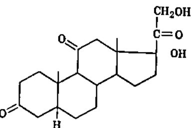
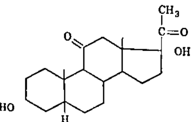


Ergosterol

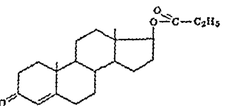
LXXXV



Δ^{16} Androsten 3-one

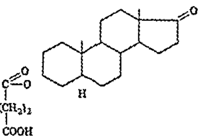
Compound Number	Structure	Systematic Name (Common Name)
LXXXVI		Pregnane-3α 11β 17α 21 tetrol 20-one (tetrahydrohydrocortisone urocortisol)
LXXXVII		Pregnane 17α 21-diol 3 11 20-trione (dihydrocortisone)
LXXXVIII		Pregnane-3α 17α-diol 11 20-dione

LXXXIX



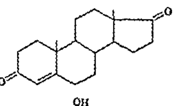
Δ^4 And oste 17β-ol 3-one propionate (te to tero e propior ate)

XC



Androstan 3α-ol 17-one succinate (an lrosterone succinate)

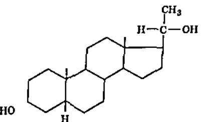
XCI



Δ An fro ten-6α-ol 3 17-dion

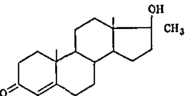
Compound Number	Structure	Systematic Name (Common Name)
XCII	NH_2, HO, H	Andro tan 3α-ol 17β amino
XCIII	CH_3, C=O, HO, H	Preguan 3α-ol 20-one (pregnanolone)
XCIV	CH_3, C=O, O	Δ^4 Pregnene-3 20 dione (progesterone)

XCV



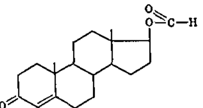
Pregnane 3α 20α-diol (pregnane [illegible] ol)

XCVI



17 Methyl Δ^4 androsten 17β-ol-3-one
(methyltestosterone 17 methyltestosterone)

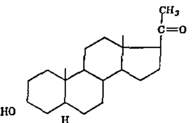
XCVII



Δ^4 Androsten 17β-ol 3-one formate (testosterone formate)

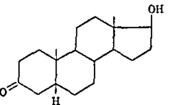
Compound Number	Structure	Systematic Name (Common Name)
XCVIII	OH, O, H	Androstan 17β-ol 3-one
XCIX	OH, HO	Δ[5] Androstene-3α 17β-diol
C	O, HO	Δ[5] Androsten 3α-ol 17 one

CI



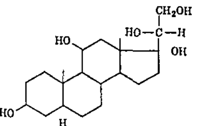
Alloj regr an 3α-ol 20-o

CII



Etiocholan 1 β-ol 3-onc

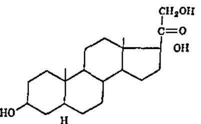
CIII



Allopregnane-3β 11β 17α 20β 21 pentol

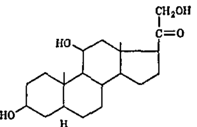
Compound Number	Structure	Systematic Name (Common Name)
CIV	CH_2OH, C=O, OH, HO, HO, H	Allopregnane-3β 11β 17α 21 tetrol 20-one
CV	CH_2OH, C=O, OH, O, HO, H	Allopregnane 3β 17α 21 triol 11 20-dione
CVI	CH_2OH, HO—C—H, OH, HO, H	Allopregnane 3β 17α 20β 21 tetrol

CVII



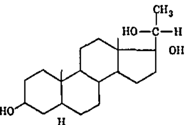
Allopregnane-3β 17α 21 triol 20-one

CVIII

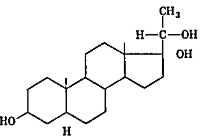
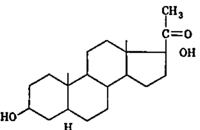
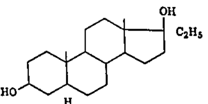


Allopregnane-3β 11β 21 triol 20-one

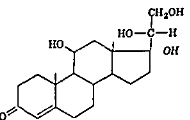
CIX



Allopregnane-3β 17α 20β triol

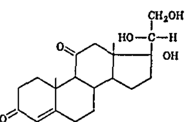
Compound Number	Structure	Systematic Name (Common Name)
CX		Allopregnane-3β 17α 20α triol
CXI		Allopregnane-3β 17α-diol 20-one
CXII		17 Ethylandrostane-3β 17β-diol

CXIII



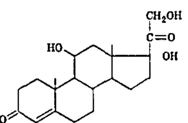
Δ^4 I r gn ne-11β 17α 20β 21 tetrol 3-one

CXIV



Δ^4 I regnene-17α 20β 21 triol 3 11-dione

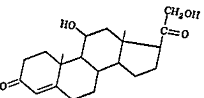
CXV



Δ^4 I regnene 11β 17α 21 triol 3 20-dione (hydrocortisone cortisol)

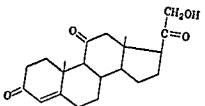
Compound Number	Structure	Systematic Name (Common Name)
CXVI	CH_2OH, C=O, OH; O (positions 3, 11)	Δ^4 Pregnene 17α 21-diol 3 11 20 trione (cortisone)
CXVII	CH_2OH, C=O, OH; O (position 3)	Δ^4 Pregnene 17α 21-diol 3 20-dione (17α hydroxy 11-desoxycorticosterone 11 desoxycortisol)
CXVIII	CH_2OH, HO—C—H; O (positions 3, 11)	Δ^4 Pregnene-20β 21 diol 3 11-dione

CXX

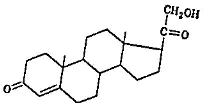


Δ^4 Pregnene-11β 21-d ol 3 20-1 o e (corticosterone)

CXXI

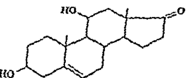
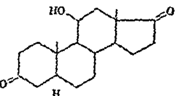
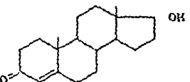
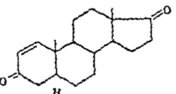


Δ^4 I regnen 21-ol 3 11 20-trione (lel y lrocorticosterone 11-del y drocorticosterone)

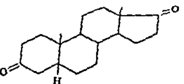
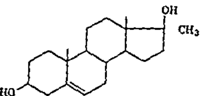
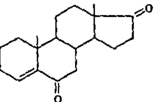


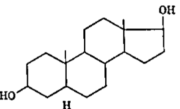
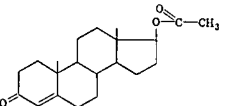
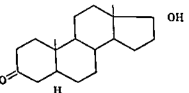
Δ^4 I regnen 21-ol 3 20-dione (desoxy corticosterone 11-desoxy cr rticosteroi e)

Compound Number	Structure	Systematic Name (Common Name)
CXXII		Allopregnane-3α 11β 17α 21 tetrol 20-one
CXXIII		Androstan 3β-ol 11 17-dione
CXXIV		Δ[4] Androsten 11β-ol 3 17 dione (11β hydroxy Δ[4] androstene 3 17-dione)

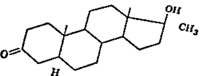
CXXV		Δ^5 Androstene-3β 11β-diol 17-one
CXXVI		Androstan 11β-ol 3 17-dione
CXXVII		Δ^4 Androsten 17α-ol 3-one (epitestosterone old name cistestosterone)
CXXVIII		Δ^1 Androstene-3 17-dione

Compound Number	Structure	Systematic Name (Common Name)
CXXII		Allopregnane-3α 11β 17α 21 tetrol 20-one
CXXIII		Androstan 3β-ol 11 17 dione
CXXIV		Δ^4 Androsten 11β-ol 3 17 dione (11β hydroxy Δ^4 androstene-3 17-dione)

CXXXII		[illegible] 17-dione
CXXXIII		17-Methyl-Δ^5-androstene-3β,17β-diol (methylandrostenediol)
CXXXIV		Δ^4-Androstene-6,17-dione

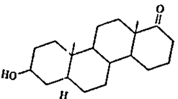
Compound Number	Structure	Systematic Name (Common Name)
CXXIX		Androstane 3β 17β-diol
CXXX		Δ^4 Androsten 17β ol 3-one acetate (testosterone acetate)
CXXXI		Androstan 17α-ol 3-one

CXXXIX

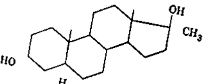


17-Methylandrostan-17β-ol-3-one

CXL



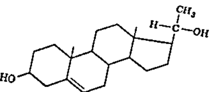
D-Homoandrostan-3β-ol-17a-one



17-Methylandrostane-3α,17β-diol

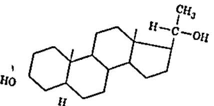
Compound Number	Structure	Systematic Name (Common Name)
CXXXV		Pregnan 3α-ol 11 20 dione
CXXXVI		Pregnane-3α 20α-diol 11 one
CXXXVII		$\Delta^{4,6}$ Androstadien 17β-ol 3-one

CXLV

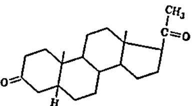


Δ^5 Preg e e 3β 20α-d l

CXLVI



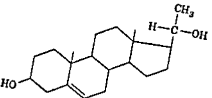
Allo]regnane-3α 20α-diol



Pregnane-3 20-dione

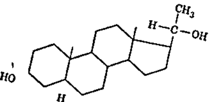
Compound Number	Structure	Systematic Name (Common Name)
CXLI		17-Ethylandrostane-3α,17β-diol
CXLII		17-Ethylandrostan-17β-ol-3-one
CXLIII		Pregnane-3β,20α-diol

CXLV

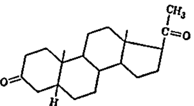


Δ^5 Pregnene 3β 20α diol

CXLVI



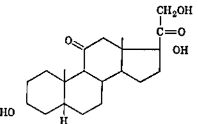
Allopregnane-3α 20α-diol



Pregnane-3 20-dione

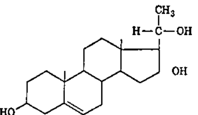
Compound Number	Structure	Systematic Name (Common Name)
CXLVII		Δ Allopregnen 20-one
CXLVIII		Equilenin
CXLIX		Estradiol 17β 3-benzoate (estradiol benzoate)

CL



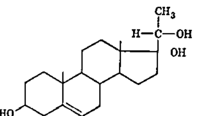
Pregnane 3α 17α 21 triol 11 20 dione

CLI



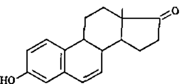
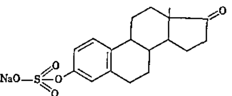
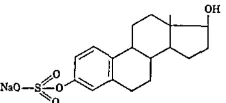
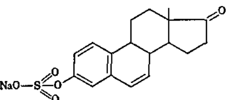
Δ^5 Pregnene-3β 16α 20α triol

CLII



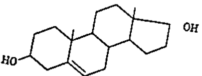
Δ^5 Pregnene-3β 17α 20α triol

Compound Number	Structure	Systematic Name (Common Name)
CLIII		3β Chloro-Δ^5 androsten 17β ol
CLIV		17 Isopregnan 3α-ol 20-one
CLV		Etiocholane-3α 17α diol

CLVI		Equilen
CLVII		Sodium estrone sulfate
CLVIII		Sodium estradiol sulfate
CLIX		Sodium equilen sulfate

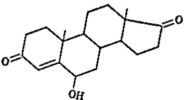
Compound Number	Structure	Systematic Name (Common Name)
CLX		Sodium cholesterol sulfate
CLXI		21 Chloro Δ^4 pregnene 3 20-dione [redacted](21 chloroproge terone)
CLXII		20 21 Epoxy Δ^4 pregnen 3-one

CLXIII



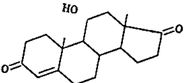
Δ^5 Androstene-3β 17α-diol

CLXIV



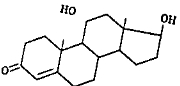
Δ^4 Androsten-6β-ol 3 17-dione

CLXV

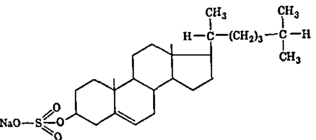
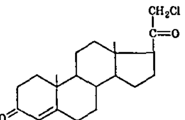
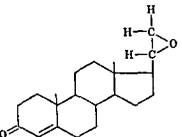


Δ^4 Androsten 11α-ol-3 17 dione

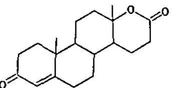
CLXVI



Δ^4 Androstene 11α 17β-diol 3-one

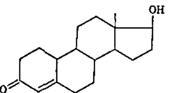
Compound Number	Structure	Systematic Name (Common Name)
CLX		Sodium cholesterol sulfate
CLXI		21 Chloro Δ^4 pregnene 3 20-dione (21 chloroprogesterone)
CLXII		20 21 Epoxy Δ^4 pregnen 3-one

CLXX



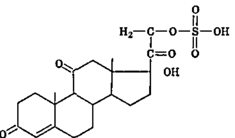
Testololactone

CLXXI



19 Nortestosterone

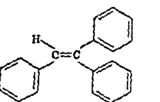
CLXXII



Δ^4 Pregnene-17α 21-diol 3 11 20-trione sulfate
(cortisone sulfate)

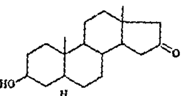
Compound Number	Structure	Systematic Name (Common Name)
CLXVII		Testosterone β cyclopentylpropionate
CLXVIII		Testosterone β-cyclohexylpropionate
CLXIX		$\Delta^{4,16}$ Pregnadiene 3,20 dione (Δ^{16} dehydroprogesterone)

CLXXVI



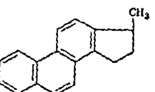
Triphenylethylene

CLXXVII

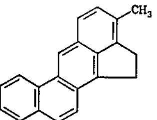
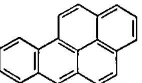
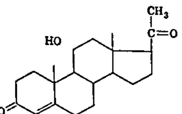


Androstan-3β-ol-16-one

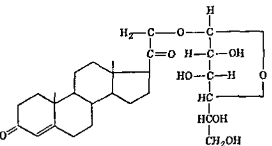
CLXXVIII



3′-Methyl-1,2-cyclopentanophenanthrene

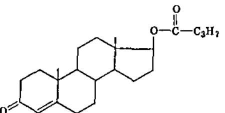
Compound Number	Structure	Systematic Name (Common Name)
CLXXIII		Methylcholanthrene
CLXXIV		1 2 Benzpyrene (benzpyrene)
CLXXV		Δ^4 Pregnen 11α-ol 3 20-dione (11α hydroxyprogesterone)

CLXXXII



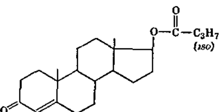
Δ^4 Pregnen 21 ol 3 20-dione 21 glucos de (desoxycortico terone glucoside)

CLXXXIII



Δ^4 Andro ten 17β-ol 3-one butyrate (testosterone butyrate)

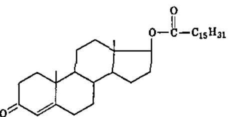
CLXXXIV



Δ^4 Androsten 17β ol 3-one i obutyrate (te tosterone i obutyrate)

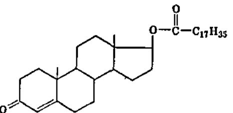
Compound Number	Structure	Systematic Name (Common Name)
CLXXIX		7-Ketocholesterol
CLXXX		Estradiol 17β dipropionate
CLXXXI		Δ^4 Pregnen 21 ol 3 20-dione acetate (desoxycorticosterone acetate)

CLXXXVIII



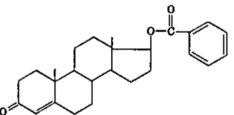
Δ^4 Androsten 17β-ol 3-one palmitate (testosterone palmitate)

CLXXXIX



Δ^4 Androsten 17β-ol-3-one stearate (te tosterone stearate)

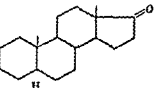
CXC



Δ^4 Androsten 17β-ol-3-one benzoate (testo terone benzoate)

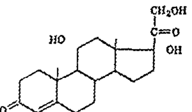
Compound Number	Structure	Systematic Name (Common Name)
CLXXXV	$O-\overset{O}{\overset{\parallel}{C}}-C_4H_9$	Δ^4 Androsten 17β-ol 3-one valerate (testosterone valerate)
CLXXXVI	$O-\overset{O}{\overset{\parallel}{C}}-C_4H_9$ (iso)	Δ^4 Androsten 17β-ol 3-one isovalerate (testosterone isovalerate)
CLXXXVII	$O-\overset{O}{\overset{\parallel}{C}}-C_9H_{19}$	Δ^4 Androsten 17β-ol 3-one decanoate (testosterone decanoate)

CXCIV



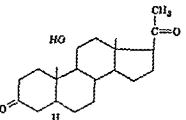
Androstan-17-one

CXCV



Δ^4-Pregnene-11α,17α,21-triol-3,20-dione
(11-epihydrocortisone, 11-epicortisol)

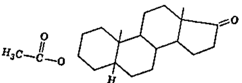
CXCVI



Pregnan-11α-ol-3,20-dione
(11α-Hydroxypregnane-3,20-dione)

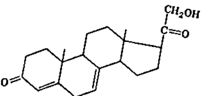
Compound Number	Structure	Systematic Name (Common Name)
CXCI	$H_3C—\overset{O}{\overset{\Vert}{C}}—O$ … $O—\overset{O}{\overset{\Vert}{C}}—C_2H_5$	$\Delta^{3,5}$ Androstadiene-3 17β-diol-3-acetate-17β propionate (testosterone-3-acetate 17 propionate)
CXCII	$H_5C_2—\overset{O}{\overset{\Vert}{C}}—O$ … $O—\overset{O}{\overset{\Vert}{C}}—C\ H$	$\Delta^{3,5}$ Andro tadiene-3 17β diol dipropionate (te tosterone dipropionate)
CXCIII	$H_3C—\overset{O}{\overset{\Vert}{C}}—O$ … $O—\overset{O}{\overset{\Vert}{C}}—C_3H_7$	$\Delta^{3,5}$ Androstadiene-3 17β diol 3-acetate 17β n butyrate (testosterone 3-acetate 17 n butyrate)

CC



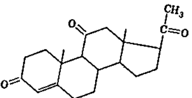
Etiocholan 3α-ol 17-one acetate

CCI

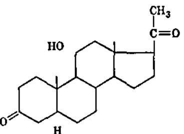
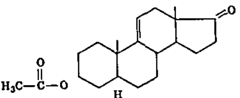
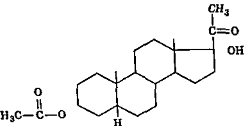


$\Delta^{4,7}$ Pregnadien 21-ol 3 20-dione

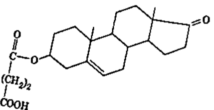
CCII



Δ^{4} Pregnene-3 11 20-trione (11 ketoprogesteron)

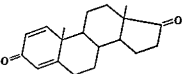
Compound Number	Structure	Systematic Name (Common Name)
CXCVII		Allopregnan 11α-ol 3 20 dione (11α Hydroxyallopregnane 3 20-dione)
CXCVIII		$\Delta^{9(11)}$ Androsten 3α-ol 17-one acetate
CXCIX		*Pregnane 3α 17α-diol 20-one-3-acetate*

CCVI



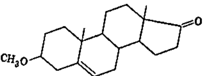
Δ^5 Androsten-3β-ol 17-one succinate
(dehydroepiandrosterone succinate)

CCVII



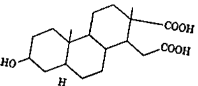
$\Delta^{1,4}$ Androstadiene 3,17-dione

CCVIII



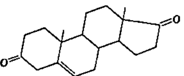
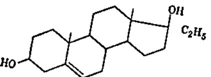
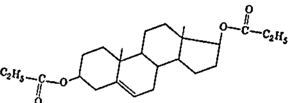
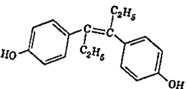
3β Methoxy Δ^5 androsten 17-one
(dehydroepiandrosterone methyl ether)

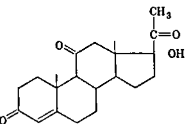
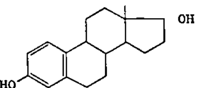
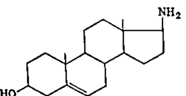
CCIX



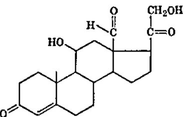
3β Hydroxyetioallobilianic acid

Compound Number	Structure	Systematic Name (Common Name)
CCIII	CH_3, C=O, HO, O	Δ^4-Pregnen-11α-ol-3,20-dione (11α-hydroxyprogesterone)
CCIV	CH_2OH, C=O, HO, O	Δ^4-Pregnene-11α,21-diol-3,20-dione (11-epicorticosterone)
CCV	CH_3, H—C—OH, OH, O	Δ^4-Pregnene-17α,20α-diol-3-one

CCXIII		
CCXIV		Δ^5 Androstene-3 17-dione
CCXV		17 Ethyl Δ^5 androstene-3β 17β-diol
CCXVI		Δ^5 Androstene-3β 17β-diol dipropionate
		*Trans* p p¹-dihydroxystilbene (diethylstilbestrol stilbestrol)

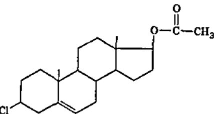
Compound Number	Structure	Systematic Name (Common Name)
CCX		Δ^4 Pregnen 17α ol 3 11 20 trione (21 desoxycortisone)
CCXI		Estradiol 17α (old name β-estradiol)
CCXII		Δ^5 Androsten 3β-ol 17β amino

CCXX



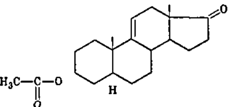
Δ^4 Pregnene 11β 21 diol 3 20-dione 18-al
(aldosterone electrocortin)

CCXXI



3β Chloro-Δ^5 androsten 17β ol acetate

CCXXII



$\Delta^{9(11)}$ Androsten 3α-ol 17-one acetate

Compound Number	Structure	Systematic Name (Common Name)
CCXVII		Allopregnane-3 20-dione
CCXVIII		Δ^5 Pregnen 3β ol 20-one acetate
CCXIX		Testosterone 17β β-diethylaminoethyl carbonate hydrochloric acid

APPENDIX B

Preparation of Urinary Extracts for 17-Ketosteroid and Androgen Assay

Introduction

As mentioned previously (Chapter 5) the 17 ketosteroids are present in freshly voided urine as water soluble complexes such as steroid

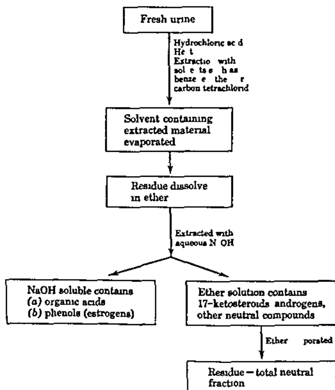


Fig 1 Preparation of the total neutral fraction of urine

in combination with sulfuric acid and/or glucuronic acid. To extract the free steroids from urine it is necessary to break the complexes so that the free compounds may be extracted with lipid solvents The

Compound Number	Structure	Systematic Name (Common Name)
CCXXIII		$\Delta^{9(11)}$ Etiocholen 3α-ol 17 one acetate
CCXXIV		9α 11α Epoxyandrostan 3α ol 17 one
CCXXV		9α 11α Epoxyetiocholan 3α-ol 17-one

The ketonic neutral fraction containing the 17 ketosteroids, can be fractionated into the α 17 ketosteroids and the β 17 ketosteroids by the use of digitonin Steroids possessing the 3β hydroxy configuration in ring A usually form insoluble digitonides with digitonin Those ketosteroids not possessing an hydroxyl group at carbon 3 or possessing a 3α hydroxy group are not usually precipitated This separation of the ketonic neutral material results in two fractions which are designated as the α ketonic neutral fraction and the β ketonic neutral fraction (Fig 2)

Preparation of Extracts for 17 Ketosteroid and Androgen Assay

In the following sections of this appendix a variety of methods which have been used for the study of 17 ketosteroids are described for the preparation of urinary extracts and their purification to various degrees

Preparation of total urinary extract

EXTRACTION PROCEDURE A (DORFMAN [1]) *The following procedure* is based on the extraction of a one liter sample of urine The specimen is preserved with 10 ml of toluene When left at a temperature of about 5°C *the urine can be kept at least one week before the* extraction procedure is started The urine is transferred to a flask and 150 ml of concentrated hydrochloric acid plus 250 ml of carbon tetrachloride are added The mixture is refluxed for 6 hours cooled and the carbon tetrachloride separated in a separatory funnel A fresh portion of 250 ml of carbon tetrachloride is added to the acidified urine and the mixture is again refluxed for 6 hours and treated as before The combined carbon tetrachloride extracts are evaporated to dryness under reduced pressure The residue constitutes the total extract Benzene may be used in place of carbon tetrachloride but the latter solvent is preferable because of the fire hazard with benzene No significant difference could be found in the amount of steroids extracted under these conditions with ether benzene or carbon tetrachloride

EXTRACTION PROCEDURE B (DORFMAN [1]) 150 ml of concentrated hydrochloric acid are added per liter of urine and the mixture is refluxed for 15 minutes After being cooled under the tap 100 grams of sodium chloride are added to help prevent emulsions during the subsequent procedure The hydrolyzed mixture is extracted three times with 250 ml portions of benzene by shaking for 5 minutes on a

crude lipid extract (total extract) contains neutral phenolic and acidic compounds Since the 17 ketosteroids are neutral compounds the total extract is distributed between a lipid solvent such as ether and aqueous alkali The neutral compounds remain in the lipid solvent and constitute the total neutral fraction (Fig 1)

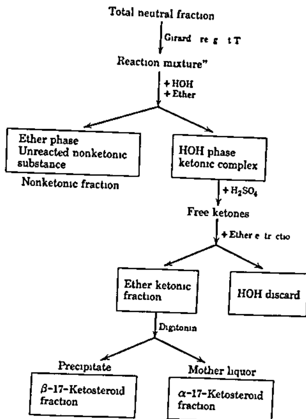


Fig 2 Preparation of ketonic and nonketonic fractions with Girard s Reagent T and preparation of α and β 17 ketosteroid fractions with digitonin

The 17 ketosteroids may be further fractionated by treatment of the total neutral fraction with the Girard reagent (trimethylacethydrazide ammonium chloride) to separate the ketonic neutral and non ketonic neutral compounds The 17 ketosteroids are present in the ketonic neutral fraction This fractionation depends upon the fact that Girard s reagent T forms water soluble derivatives with the 17 ketosteroids so that the ketone derivative may be separated from the nonketonic compounds by distribution between water and ether at low temperatures The resulting materials are designated as the ketonic neutral and nonketonic neutral fractions (Fig 2)

bined ethereal extracts after being washed three times with 20 ml portions of water are evaporated to dryness This residue constitutes the nonketonic neutral fraction To the water washings of the above ether extract 1 ml of concentrated sulfuric acid and 20 ml of ethyl ether are added After the mixture has stood for at least 2 hours at room temperature 1 ml of concentrated sulfuric acid is added to facilitate the extraction of the ketones and the mixture is extracted four times with 40-ml portions of ether The combined ethereal extracts are washed with 20 ml portions of water until the wash water is neutral in reaction The ether layer is evaporated to dryness and the residue constitutes the neutral ketonic fraction

METHOD B (PINCUS AND PEARLMAN[4]) The total neutral residue from 1 liter of urine is thoroughly dried in a Pyrex test tube over calcium chloride in a vacuum desiccator 0 5 ml glacial acetic acid and approximately 100 mg of Girard s reagent T are added The tube is loosely stoppered with cork wrapped in aluminum foil and placed in an oil bath at 90 to 100 C for 20 minutes The tube is cooled 15 ml of ice water are added and the reaction mixture is immediately transferred to a small separatory funnel Sufficient 10 per cent sodium hydroxide is added to neutralize nine tenths of the acetic acid The *mixture is extracted with three 20 ml portions of ether An aqueous* wash is combined with the main aqueous fraction The ether layer contains the nonketonic compounds and may be discarded The aqueous fraction which contains the ketonic compounds (17 keto steroids included) is acidified with 3 ml of concentrated hydrochloric acid allowed to stand at room temperature for 2 hours and then extracted three times with 20 ml portions of ether The ether is washed with 10 ml of 2 5 per cent sodium carbonate and three times with 10 ml portions of water or until the wash water is neutral in reaction The ether is evaporated to dryness and the residue constitutes the neutral ketonic fraction

Preparation of α and β neutral ketonic fractions

METHOD A (FRAME[5]) The total neutral fraction or the neutral ketonic fraction from two liters of urine (containing about 15 mg of 17 ketosteroids) is dissolved in absolute ethanol and transferred quantitatively to a calibrated 15 ml centrifuge tube and warmed To the ethanol solution is added a warm solution of digitonin in such proportions of absolute alcohol and water that the final concentration of digitonin is 1 per cent in 90 per cent ethanol At least 14 mg of digitonin should be allowed for each milligram of 17 ketosteroid expected in the test solution The tube is stoppered centrifuged for 10

mechanical shaking machine After each extraction the mixture is separated in a separatory funnel The three *benzene* extractions are combined washed once with 100 ml of *water and the* benzene layer evaporated to dryness *in vacuo The residue constitutes the total* extract

EXTRACTION PROCEDURE C (PINCUS) 150 ml of concentrated hydrochloric acid per liter of urine are added and the mixture is refluxed *for 7 minutes The mixture is extracted four times with 200 ml* portions of ethyl ether in a separatory funnel The combined ethyl ether extractions can be evaporated to dryness to constitute the total extract or kept in the ether solution for subsequent purification as described *under preparation of total neutral fraction*

EXTRACTION PROCEDURE D (TALBOT ET AL [3]) One liter of urine is brought to *p*H 1 with concentrated sulfuric acid and sufficient 50 per cent sulfuric acid added to bring the total acidity to 5 per cent by *volume The acid urine mixture is heated under reflux for one half hour* The acidified hydrolyzed urine is transferred to a Kutscher Steudel type of continuous extractor and extracted for 24 *hours* with ether The ether extract can be evaporated to dryness to constitute *the total extract or evaporated to a convenient volume for subsequent* purification

Preparation of total neutral extract

The procedure is based on the total extract from one liter of urine The residue of the total extract derived from one of the above procedures is dissolved in 100 ml of ethyl ether and transferred to a separatory funnel The ether is extracted three times with 25 ml portions of $2N$ sodium hydroxide to remove the phenolic and acid compounds and with three 25 ml portions of distilled water or until the water washings show a neutral reaction to litmus The ether layer is evaporated to dryness and the residue constitutes the total neutral fraction The aqueous layer contains the estrogen fraction and may be processed for their assay if desired

Preparation of neutral ketonic fraction

METHOD A (TALBOT [3]) The dry residue of the total neutral fraction derived from a liter of urine is dissolved in 4 ml of 95 per cent ethanol and after addition of 0 5 ml of glacial acetic acid and 0 5 gram of Girard s reagent T the solution is refluxed for 1 hour on a water bath After the solution has been cooled and 40 grams of ice added 3 ml of $2N$ sodium hydroxide are added and the mixture is extracted four times with 40 ml portions of ethyl ether The com

bined ethereal extracts after being washed three times with 20 ml portions of water are evaporated to dryness This residue constitutes the nonketonic neutral fraction To the water washings of the above ether extract 1 ml of concentrated sulfuric acid and 20 ml of ethyl ether are added After the mixture has stood for at least 2 hours at room temperature 1 ml of concentrated sulfuric acid is added to facilitate the extraction of the ketones and the mixture is extracted four times with 40 ml portions of ether The combined ethereal extracts are washed with 20 ml portions of water until the wash water is neutral in reaction The ether layer is evaporated to dryness and the residue constitutes the neutral ketonic fraction

METHOD B (PINCUS AND PEARLMAN[4]) The total neutral residue from 1 liter of urine is thoroughly dried in a Pyrex test tube over calcium chloride in a vacuum desiccator 0 5 ml glacial acetic acid and approximately 100 mg of Girard s reagent T are added The tube is loosely stoppered with cork wrapped in aluminum foil and placed in an oil bath at 90 to 100°C for 20 minutes The tube is cooled 15 ml of ice water are added and the reaction mixture is immediately transferred to a small separatory funnel Sufficient 10 per cent sodium hydroxide is added to neutralize nine tenths of the acetic acid The mixture is extracted with three 20 ml portions of ether An aqueous wash is combined with the main aqueous fraction The ether layer contains the nonketonic compounds and may be discarded The aqueous fraction which contains the ketonic compounds (17 keto steroids included) is acidified with 3 ml of concentrated hydrochloric acid allowed to stand at room temperature for 2 hours and then extracted three times with 20 ml portions of ether The ether is washed with 10 ml of 2 5 per cent sodium carbonate and three times with 10 ml portions of water or until the wash water is neutral in reaction The ether is evaporated to dryness and the residue constitutes the neutral ketonic fraction

Preparation of α and β neutral ketonic fractions

METHOD A (FRAME[5]) The total neutral fraction or the neutral ketonic fraction from two liters of urine (containing about 15 mg of 17 ketosteroids) is dissolved in absolute ethanol and transferred quantitatively to a calibrated 15 ml centrifuge tube and warmed To the ethanol solution is added a warm solution of digitonin in such proportions of absolute alcohol and water that the final concentration of digitonin is 1 per cent in 90 per cent ethanol At least 14 mg of digitonin should be allowed for each milligram of 17 ketosteroid expected in the test solution The tube is stoppered centrifuged for 10

minutes at about 200 rpm and the supernatant poured off into a 250 ml separatory funnel The precipitate which contains the beta fraction is washed three times with 10 ml portions of ether with stirring and centrifuging after each addition The ether washings are added to the supernatant on the separatory funnel The combined ether extracts are washed three times with 25 ml portions of water the ether solution is drawn into a flask evaporated under reduced pressure and *dried in a desiccator* over calcium chloride This fraction contains the material which is not precipitable by digitonin and which is designated the alpha fraction

The *precipitate remaining in the centrifuge tube (beta fraction)* is dissolved in 0 5 ml of dry pyridine and heated for 3 minutes in a hot water bath After the mixture is cooled 10 ml of anhydrous ether are added to precipitate the digitonin and the *tube is centrifuged* for 10 minutes The supernatant containing the beta fraction is poured into a 250 ml separatory funnel and the pyridine ether treatment of the precipitate is repeated The remaining precipitate is washed twice with 10 ml of ether with stirring and centrifuging each time The combined ether pyridine solution is washed three times with 10 ml portions of 2 N sulfuric acid to remove the pyridine and three times with 25 ml portions of water to remove the sulfuric acid The ether solution is evaporated to dryness the residue constitutes the β ketonic neutral fraction

When the starting volume is greater than 3 ml that is when more than 30 mg of digitonin are required to precipitate the beta fraction it is preferable to carry out the separations in a 50 ml centrifuge tube The procedure here is identical with that outlined above except that 25 ml portions of ether 1 0 or 1 5 ml portions of pyridine and 20 to 25 ml portions of acid are used

METHOD B (BUTT ET AL [6]) *An amount of urine containing* 1 0 to 1 5 mg of 17 ketosteroids is transferred to a graduated centrifuge tube and evaporated to dryness under reduced pressure Warm digitonin *solution* [0 75 ml of 1 per cent solution in 90 per cent (v/v) ethanol] is added and the mixture is quickly heated to boiling in order to dissolve as much of the material as possible The tube is stoppered and left in a refrigerator overnight A total of 10 ml of peroxide free ether is then added in small portions with stirring after each addition and the precipitated digitonin and digitonides are allowed to flocculate before the last 2 to 3 ml are added After centrifuging the supernatant is decanted into a separatory funnel and the *precipitate is* washed three times with 5 ml portions of ether with stirring and centrifuging each time The combined supernatants are washed three

times with 5 ml portions of water and are then evaporated to dryness under reduced pressure The residue constitutes the α ketonic fraction The precipitate containing the β ketonic substances is dissolved in 0 25 ml of dry pyridine warmed to 60 to 70 C for 3 minutes cooled and 5 ml of ether added in portions stirred and the precipitate is allowed to flocculate The mixture is centrifuged and the precipitate is again treated with pyridine and ether and the final residue washed twice with 5 ml portions of ether The combined extracts are washed twice with 5 ml portions of water and then evaporated to dryness under reduced pressure The residue is the β ketonic fraction

Micro extraction methods

Micro methods have been described for the determination of 17 ketosteroids in total neutral extracts of small volumes of urine These methods are convenient and particularly desirable for clinical work when further fractionation is deemed unnecessary Two micro methods of Drekter et al[7, 8] have been described Method A[7] has been employed by various workers and the results are included in the literature tabulations (Chapter 20) Method B[8] has more recently been reported and since it has considerable merit it is also included here The micro method of Hamburger[9] is also presented

METHOD A (DREKTER ET AL[7]) Ten ml of urine and 3 ml of concentrated HCl are placed in a 125 ml Erlenmeyer flask and the flask is stoppered with a Pyrex flat head stopper The flask is heated in a water bath at 80 C for 10 minutes and 5 ml of the hydrolysate are cooled and transferred to a 125 ml separatory funnel Twenty ml of ether are added and the funnel is shaken for 30 seconds The extracted urine is removed The ether is washed once with 10 ml of 10 per cent NaOH and once with 10 ml of distilled water and shaken for 10 seconds with each wash Five ml of ether are removed evaporated and assayed by means of the Zimmermann reaction (see Drekter Method B)

METHOD B (DREKTER ET AL[8]) Ten ml of urine are transferred to a 30 ml Pyrex centrifuge bottle Three ml of concentrated HCl are added and the bottle containing the mixture is placed in a water bath at 100°C (With each batch of determinations a method blank is set up by substituting 10 ml of water for urine and following through with the entire procedure) The bottle is removed from the water bath after 10 minutes and cooled Ten ml of ethylene dichloride are added and the bottle is stoppered and shaken for 15 minutes The bottle is centrifuged and the top aqueous layer is aspirated The ethylene

dichloride extract is poured through Whatman's No 1 filter paper into a 20 ml bottle Approximately 20 pellets of sodium hydroxide are added and the bottle is stoppered and shaken for 15 minutes The solution is filtered through Whatman's No 1 filter paper Two ml of the ethylene dichloride solution are transferred into a test tube and dried in a water bath at 100 C until all traces of solvent have been evaporated When cool 0 4 ml of 1 per cent metadinitrobenzene in absolute ethanol is added and the tube is rotated to dissolve the dried material Then 0 3 ml of 8 *N* potassium hydroxide is added the contents are mixed and placed in a water bath at 25°C after which 0 4 ml of the standard [5 mg of dehydroepiandrosterone (XXIII) in 100 ml of absolute ethanol] is transferred to a test tube and the metadinitrobenzene solution is added as above Similarly a Zimmermann reagent blank is prepared After exactly 25 minutes 2 ml of 75 per cent ethanol are added The Zimmermann reagent blank is set at 100 per cent transmission The standard is read Next the method blank is set at 100 per cent transmission The unknown is now read The standard is equivalent to 10 mg per liter of 17 ketosteroids expressed as dehydroepiandrosterone (XXIII) and the calculation of the unknowns is based upon the recommendation of the manufacturer of the colorimeter employed If the colorimeter to be used has a capacity greater than 2 7 ml then a larger aliquot of the ethylene dichloride extract can be taken and the amounts of reagents used for the Zimmermann test are increased as needed

METHOD C (HAMBURGER[9]) An amount of urine equal to one fiftieth of a 24 hour output is measured out from a 10 ml pipette graduated to 0 1 ml into a flask (if below 10 ml water is added to 10 ml) From a 1 ml pipette graduated to 0 01 ml 10 volume per cent of 40 per cent H_2SO_4 are added to the urine

Simultaneous Hydrolysis and Benzene Extraction Forty ml of benzene (crystallizable) are added to the acidified urine The boiling is performed on an electric hot plate in 450 ml flat bottomed culture flasks fitted with reflux condensers An electric hot plate with a diameter of 22 cm leaves space for three of the flasks and the reflux condensers can be connected serially When the temperature on the hot plate is kept moderate the urine boils smoothly especially when a piece of glass is put into the flask The advantage of a flask of this shape is the extended contact surface between the urine and the benzene layer with 20 ml of urine the contact surface is about 80 sq cm whereas the height of the urine layer is merely ¼ cm The liberated steroids therefore pass very rapidly to the benzene layer Refluxing with benzene for various periods of time showed that most of the

steroids are removed within 5 minutes Since the hydrolysis usually is complete after 25 minutes the total time for the benzene refluxing should be 30 minutes

After being refluxed for 30 minutes the mixture is cooled under running tap water and the benzene extract is freed from nonspecific chromogenic substances and phenols by extracting once with saturated $NaHCO_3$ solution twice with 2 *N* NaOH solution and twice with water each of the washings being made with about 10 ml of solution After being dried with anhydrous sodium sulfate the benzene extract is filtered and evaporated to dryness over a boiling water bath under reduced pressure The residue may now be analyzed by the Zimmermann reaction (Appendix D)

Fractionation of Individual 17 Ketosteroids

Callow and Callow[10] separated androsterone (XXV) dehydroepiandrosterone (XXIII) and etiocholan-3α ol 17 one (XXII) by a chromatographic method using aluminum oxide as the adsorbent and mixtures of carbon tetrachloride and ethanol for the development and elution This method was sufficient for semiquantitative work and for qualitative identification of this limited group of 17 ketosteroids With the discovery that additional 17 ketosteroids were present in human urine it was desirable to have a method for the quantitative determination of the individual constituents Dingemanse et al[11] published such a method employing alumina as the adsorbent and benzene and benzene ethanol mixtures for elutions 17 Ketosteroid determinations were done on the individual eluates The individual components were identified by the solvent fraction in which they were found as compared to reference steroids and by isolation of crystalline material from specific fractions This technique was used with modification by Robinson and Goulden[1] Devis[13] Pond[4] and Rubin et al[15]

This technique suffers from the inherent difficulties in obtaining standardized adsorbents and sharp separations of individual components

Since most procedures of urine extraction employ heat and acid such compounds as 11 hydroxyandrosterone (XXXIV) and etiocholane 3α 11β diol 17 one (XXXVII) are dehydrated to form the Δ^9 dehydro artifacts These artifacts cannot be separated from their related reduced steroids androsterone (XXV) and etiocholan 3α ol 17-one (XXII) by these adsorption chromatographic procedures

Two typical methods are described

Method A (Robinson and Goulden [12])

The total neutral extract equivalent to 5 mg of 17 ketosteroids is dissolved in 50 ml of dry thiophene free benzene

Alumina standardized with Sudan red and Sudan yellow is suitable for the chromatographic separations Sudan red (20 mg) and Sudan yellow (20 mg) both purified by recrystallization are dissolved in 10 ml of benzene and the solution made up to 50 ml with low boiling petroleum ether For standardization 1 ml of this dye *solution is adsorbed on a column 50 by 14 mm prepared from a sus* pension of the alumina (7 grams) in benzene petroleum ether (1 4) and eluted with 50 ml of the same mixed solvent The alumina is considered to have suitable absorptive power when the yellow band reaches the bottom of the column while the red band moves down *about 10 mm*

The alumina columns for absorption of the urine extracts are pre pared in tubes of 14 mm internal diameter fitted with taps and a plug of cotton wool is inserted above the tap as support The alumina (13 0 grams) is poured into the tube in benzene suspension and packing takes place by gravity alone giving a column about 10 cm high with space for 60 to 70 ml of solvent above The benzene level is allowed to fall to the top of the alumina and the solution of extract is then poured on The benzene eluate constitutes fraction 0 Elution is continued with (1) 350 ml of benzene (2) 1 2 liters of 0 1 per cent (v/v) ethanol in benzene (3) 500 ml 0 5 per cent (v/v) ethanol in benzene and (4) 100 ml of ethanol The tube above the alumina is kept full of liquid except when changing eluents and the eluate is collected in 50 ml fractions numbered from 1 to 43

The fractions are evaporated to dryness each taken up in 2 ml of ethanol and the 17 ketosteroid content is estimated by the Zimmer mann reaction A graph *is then constructed with abscissas correspond* ing to the serial number of the eluate fraction and the 17 ketosteroid values are plotted as ordinates The peaks give the individual com ponents eight of which have been visualized and five have been identified

Method B (Rubin et al [15])

The column used for chromatography consists of a 50 ml bulb with a side arm and a long neck (4 5 cm) attached to Pyrex tubing approximately 19 cm in length and 1 cm in inside diameter To this was attached a section about 2 cm in length and 0 5 cm inside di ameter which was joined to a number 2 stopcock A plug of glass

wool is inserted at the point where the column narrowed Silica gel (Davison Chemical Corporation mesh size through 200) is weighed rapidly into a small beaker (1000 parts of silica gel for each part of dried extract) and immediately wet with a mixture of 1 part of an hydrous benzene (Merck Reagent Grade or Bakers Analyzed) and 3 parts of petroleum ether (Mallinckrodt Chemical Company redis tilled) The column is prepared as a slurry using a total of 100 ml of the 1 3 benzene petroleum ether mixture (fraction 1) Positive ni trogen pressure is applied through the side arm during packing the neck of the bulb being stopped with a rubber stopper covered with aluminum foil A plug of glass wool is placed on top of the column before the addition of the urine extract After the addition of the urine extract the nitrogen pressure is regulated so that the time for collecting 40 ml of eluate is about 5 to 8 minutes With more polar solvent mixtures this rate could not be exceeded without causing the stopper to be pushed from the neck of the bulb

The α ketonic urine fractions to be chromatographed are stored in a desiccator over CaCl until immediately before they are placed on the column They are then dissolved in 25 ml of benzene and 75

TABLE 1

CHROMATOGRAPHIC FRACTIONS USING RUBIN ET AL[15] PROCEDURE

(40 ml Fractions)

Fraction Numbers	Solvent Mixture
1–6	1 3 Benzene petroleum ether
7–11	1 1 Benzene petroleum ether
12–16	3 1 Benzene petroleum ether
17–21	Benzene
22–41	3 97 Ethyl ether benzene
42–85	1 19 Ethyl ether benzene
86–95	1 9 Ethyl ether benzene
96–105	3 17 Ethyl ether benzene
106–126	1 4 Ethyl ether benzene
127–145	1 1 Ethyl ether benzene

ml of petroleum ether are added at the last minute to minimize pre cipitation Aliquots for colorimetry are removed and an aliquot of the solution estimated to contain 4 to 8 mg of 17 ketosteroids (by Zimmermann) is poured into the column Fraction 2 consists of this aliquot volume plus the first of a series of five 40 ml portions of 1 3 benzene petroleum ether The standard chromatographic elution pro cedure finally adopted is shown in Table 1 Redistilled anhydrous ether (Mallinckrodt Analytical Reagent) is used in the ether benzene

fractions A total of 145 fractions is collected over several working days The column is tightly stoppered overnight The column is never left overnight while being eluted with petroleum ether mixtures or 1 1 ether benzene

The eluates are collected in 50 ml wide mouthed Florence flasks and evaporated to dryness on a steam bath They are made up to 10 ml with 95 per cent ethanol and 1 and 4 ml aliquots are taken for the Zimmermann reaction If the amount of color in the 4 ml aliquot is insignificant the fraction is considered not to contain any significant amount of 17 ketosteroids The micrograms of 17 keto steroid in the fraction are plotted against the fraction number and the amount of material in each peak is calculated and reported as the percentage it represents of the total amount of 17 ketosteroid put on the column Because so many aliquots are removed for 17 ketosteroid analysis during the preparation of the extracts for chromatography and for comparison between urine extracts this is considered prefer able to reporting the various components in absolute amounts though a calculation of the absolute amounts in a 24 hour urine could easily be made from the percentage distribution

Method C (Rubin et al [16, 17])

With this method it is possible to separate the six principal α 17 ketosteroids which then can be quantitatively determined in the usual manner by the Zimmermann method (Chapter 6 and Ap pendix C)

PREPARATION OF CHROMATOGRAMS Whatman No 1 filter paper is cut into strips 14 or 16 cm wide and 56 cm long These strips are washed in a Soxhlet apparatus with 1 1 methanol benzene for approxi mately 48 hours For quantitative paper chromatograms these strips are cut as shown in Figs 3 and 4 From each 16 cm strip two quantitative strips of 6 cm each and one qualitative strip of 1 cm (for crystalline standards) are obtained The 6 cm strips are ruled vertically 2 mm from each edge and a 2 mm strip is marked down the center These 2 mm strips are used for locating the zones of Zimmermann reacting material and stapled back into their original positions in the chromatogram all being mounted on a sheet of paper The remaining areas of these zones 5 4 cm in width and correspond ing in length to the Zimmermann reacting zone on the 2 mm strips are used for elution and quantitative determinations The 14 cm sheets yield four 2 cm strips and one 1 cm strip The 2 cm strips are also ruled off 2 mm from each edge The area remaining for quanti tative determination was 1 6 cm in width

Just before the urine extracts or crystalline steroids are put on the paper the paper is impregnated with a 1 1 mixture of either propylene glycol and methanol or phenyl Cellosolve and methanol The

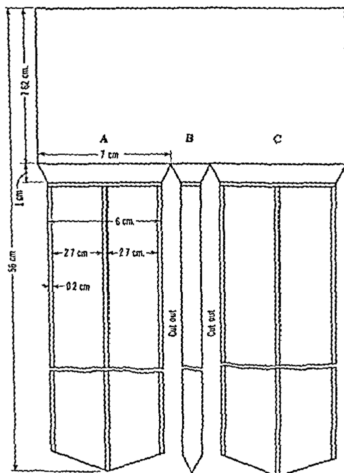


Fig 8 Preparation of filter paper for quantitative determination of individual 17 ketosteroids (Rubin et al [16 17])

excess is removed by blotting For reproducible results these two mixtures should be freshly prepared

The solutions for quantitative determination are made up in benzene and applied at the starting line as evenly as possible across the width of the strip using micropipettes (usually 100 μl) and drying the solution on the paper with a stream of nitrogen Ten μl aliquots of each solution are removed for quantitative Zimmermann

fractions A total of 145 fractions is collected over several working days The column is tightly stoppered overnight The column is never left overnight while being eluted with petroleum ether mixtures or 1 1 ether benzene

The eluates are collected in 50 ml wide mouthed Florence flasks and evaporated to dryness on a steam bath They are made up to 10 ml with 95 per cent ethanol and 1 and 4 ml aliquots are taken for the Zimmermann reaction If the amount of color in the 4 ml aliquot is insignificant the fraction is considered not to contain any significant amount of 17 ketosteroids The micrograms of 17 keto steroid in the fraction are plotted against the fraction number and the amount of material in each peak is calculated and reported as the percentage it represents of the total amount of 17 ketosteroid put on the column Because so many aliquots are removed for 17 ketosteroid analysis during the preparation of the extracts for chromatography and for comparison between urine extracts this is considered prefer able to reporting the various components in absolute amounts though a calculation of the absolute amounts in a 24 hour urine could easily be made from the percentage distribution

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matograms give satisfactory resolution at temperatures ranging from 23 to 42° The times of development will be discussed in detail in connection with chromatography of the urine extracts The propylene glycol chromatograms are allowed to dry by hanging them in the air at room temperature but the phenyl Cellosolve chromatograms require drying in an oven at 90°C for approximately 2 hours (until all odor of phenyl Cellosolve has disappeared) as small traces of phenyl Cellosolve interfere with the Zimmermann reaction

17 Ketosteroid containing zones from the 6-cm strips are eluted quantitatively by allowing them to stand overnight in 95 per cent ethanol and washing them repeatedly The ethanol is removed in vacuo and all samples are made up to 10 ml in benzene before aliquots are taken for analysis The zones from the 2 cm strips are not eluted quantitatively They are placed overnight in test tubes containing 10 ml. of 95 per cent ethanol and aliquots are taken directly from this solution These steroids are recovered in amounts ranging from 85 to 117 per cent after application of amounts as low as 90 μg The standard errors seen in the averages of five to eight runs in which androsterone (XXV) and etiocholan-3α ol 17 one (XXII) are separated from each other range from 2.5 to 6 per cent of the amount of material recovered

PREPARATION AND CHROMATOGRAPHY OF URINE EXTRACTS The urines are hydrolyzed by boiling for 8 minutes with 15 per cent volumes of hydrochloric acid and extracted with ether (see p 527) After separation with the Girards reagent (see p 528) the digitonin nonprecipitable (or α) fraction of the ketonic extracts is prepared (p 529) After determination of the 17 ketosteroid content by the Zimmermann reaction (Appendix D) in terms of dehydroepiandrosterone (XXIII) the remainder of the extract is transferred with benzene to a 3 ml screw-capped vial and dried by heating in a water bath at 90 to 95 C under a stream of nitrogen Just before the urinary extract is placed on paper it is dissolved in a volume of benzene such that 1 0 mg or less of 17 ketosteroid (by Zimmermann reaction) is contained in 100 μl of solution If the urinary extract contains 4 to 6 5 mg of 17 ketosteroid it is dissolved in 0 65 ml of benzene If fewer than 4 mg are available for analysis the extract is dissolved in 0 35 ml. of benzene and the necessary changes in the routine technique are indicated in the proper places Two 10-μL aliquots are taken from each urine extract for quantitative Zimmermann determination It must be known exactly how much 17 ketosteroid was put on each chromatogram in order to calculate back to the daily output of the various components

determinations (see Appendix D) The standard reference compounds are placed on the 1 cm strip the exact amounts not being determined A minimum of 5 μg was used for the reference standard to insure visualization with the Zimmermann reagent

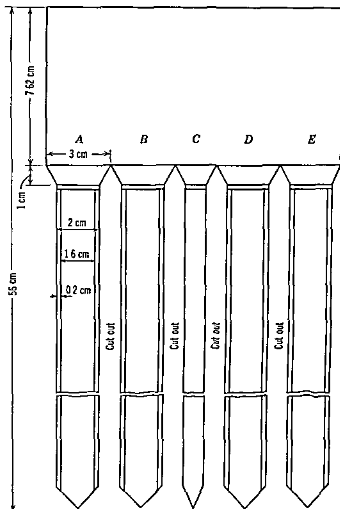


Fig 4 Preparation of filter paper for quantitative determination of individual 17 ketosteroids (Rubin et al [10 17])

Descending chromatograms were run with as mobile phase heptane previously equilibrated with either phenyl Cellosolve or propylene glycol The tanks are sealed with starch glycerol paste [18] It is essential to run the heptane phenyl Cellosolve chromatograms in a tank maintained at 23° ± 2 C The heptane propylene glycol chro

proceed for 5 hours at 5 to 7 C The material is then washed into a 125 ml separatory funnel with about 30 ml of ethyl acetate The ethyl acetate is washed with 5 per cent sodium bisulfite 5 per cent sodium bicarbonate and then with water until neutral to litmus The ethyl acetate is removed in vacuo the residue is transferred quantitatively with benzene to a 15 ml centrifuge tube and the benzene is removed The residue is applied in benzene solution to a 2 cm strip and chromatographed for 24 hours in the heptane propylene glycol system Crystalline androsterone (XXV) is used for a reference standard The major zone moving slower than androsterone (XXV) which appears in these chromatograms has been shown by infrared analysis to be the 9 11 epoxide of androsterone (CCXXIV) Repeated studies of the perbenzoic acid oxidation have demonstrated that the amount of epoxide determined by the foregoing procedure represents 81 ± 2 5 per cent of the amount of $\Delta^{9(11)}$ androsten-3α ol 17 one (LIV) present before oxidation From this it is possible to calculate the amount of the compound excreted per day The daily androsterone (XXV) excretion then is the value calculated from the androsterone (XXV) zone minus the value of the $\Delta^{9(11)}$ unsaturated compound and plus the daily value of the Δ^{2} ^{3} androsten 17 one (LII)

(c) The etiocholan 3α ol 17 one (XXII) zone is treated similarly to the androsterone (XXV) zone A 48 hour oxidation time is necessary for optimum oxidation of $\Delta^{9(11)}$ etiocholen-3α ol 17 one (LV) The chromatogram of the oxidized material is developed for 48 hours The major zone appearing on oxidation of $\Delta^{9(11)}$ etiocholen-3α ol 17 one (LV) is the 9(11) epoxide (CCXXV) The oxidation product accounts for 68 ± 1 3 per cent of the starting material under the conditions defined

(d) When the total amount of 17 ketosteroid is less than 4 mg and the volume of benzene solution only 0 35 ml the zone from the 24-hour chromatogram between the etiocholan 3α ol 17 one (XXII) zone and the starting line is eluted quantitatively The eluted material is then chromatographed on a 2 cm strip for 72 hours in heptane propylene glycol

2 *From the 72 Hour Chromatogram* The following components are obtained from analysis of the 72 hour chromatogram androstan 3α ol 11 17 dione (XXXV) etiocholan 3α ol 11 17 dione (XXXVI) and an unresolved residue which gives an atypical brownish Zimmermann color When any significant concentration of 11 hydroxylated 17 ketosteroids is present they can also be seen and determined in this unresolved residual zone

The aliquots taken for analysis of the components are based on information as to the expected order of magnitude of the individual components Four hundred μl of solution are applied to each 6 cm strip and the chromatograms are allowed to develop for 24 hours in the heptane propylene glycol system All effluent is caught in a small beaker Two hundred μl are applied to a 2 cm strip and the chromatograms are developed for 72 hours in heptane propylene glycol (When the total volume of solution is only 0 35 ml 300 μl are applied to the 6 cm strip and no 2 cm chromatogram is prepared) After the Zimmermann positive zones are determined the fractions are worked up as follows

1 *From the 24 Hour Chromatogram* (*a*) All material running faster than androsterone (XXV) is eluted quantitatively from the paper with 95 per cent ethanol and combined with the effluent After evaporation of the ethanol the material is transferred with benzene to a 15 ml centrifuge tube and dried in the water bath under nitrogen This material is then applied quantitatively to a 2 cm strip impregnated with phenyl Cellosolve methanol and allowed to run for 18 hours in the heptane phenyl Cellosolve system The effluent is again collected and the Zimmermann values for the effluent are added to the figure determined from the zone ascribed to $\Delta^{\text{ or }3}$ androsten 17 one (LII) which is usually at the end of the strip The other compounds determined in this chromatogram are 3β chloro Δ^5 androsten 17 one (XXIV) the component termed II a mixture of the 3α acetoxy etiocholan 17 one (CC) and 3α acetoxy $\Delta^{9(11)}$ etiocholen 17 one (*CCXXIII*) *and some small amount of androsterone* (*XXV*) *remain*ing at the starting line whose value can be added to that of the androsterone (XXV) zone Instead of being eluted quantitatively the cut out zones are placed in 10 ml of ethanol for 16 or more hours and aliquots taken for quantitative determination

(*b*) The androsterone (XXV) zone is eluted quantitatively with ethanol The ethanol is evaporated and the residue is dissolved in 10 ml of benzene Aliquots of 0 25 and 0 5 ml are taken for quantitative Zimmermann determinations and 8 5 ml are dried down in a 15 ml centrifuge tube under nitrogen After the Zimmermann content of the material in the centrifuge tube has been determined sufficient perbenzoic acid dissolved in benzene is added to the dried residue to oxidize the $\Delta^{9(11)}$ androsten 3α ol 17 one (LIV) to the 9 11 epoxide (CCXXIV) The solution of perbenzoic acid contains approximately 23 mg per ml and 0 2 ml of perbenzoic acid solution is added for each 500 μg of combined androsterone (XXV) and $\Delta^{9(11)}$ androsten 3α *ol 17 one* (*LIV*) *The reaction is permitted to*

APPENDIX C

Androgen Bioassay Methods

Capon Methods

The capon's comb has been used extensively as a test object for the assay of androgenic activity. The comb is normally under the control of the male sex hormone and after castration of the cock the comb *involutes and maintains a constant size over a long period of time. The administration of androgens to these animals restores the comb* to its normal size. Although the White or Brown Leghorn is usually employed, the English Game Bantam has also been found to be a sensitive test object. Heavier breeds such as the Barred Rock and Rhode Island Red are less responsive to androgens.

Caponizing

Cockerels approximately 6 weeks of age are anesthetized with ether and placed on their sides. An incision is made between the last two ribs, the muscle layer is divided, and the incision pulled apart with small retractors. The testes are found close to the midline of the posterior abdominal wall alongside the vena cava. The capsule enclosing the testis is cut and the gonad removed. No ligature is required. *Care must be exercised not to crush the testis and leave tissue* in the animal. The incision is closed by sewing and the second testis removed in a similar fashion on the other side. The animals are watched for evidence of remaining testicular tissue as indicated by continued comb growth. If this occurs the animals are discarded; otherwise they may be used for assay in about 6 months.

Intramuscular injection methods

At the start of an assay the sum of length plus height (L + H) of each comb is determined with a millimeter rule. It is well to record the exact barble used for measurement of height. Injections of extract dissolved in vegetable oil are made intramuscularly in 1 ml doses for

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TABLE 1

SUMMARY OF ANDROGEN METHODS

(Capon's Comb—Intramuscular Injection)

Material	Relationship	Duration of Test (days)	Slope (b)	Index of Precision (λ)	Sensitivity (mg)	Reference
Androsterone (XXV)	Log dose—comb growth	3	8.00	0.180	0.3	Greenwood et al[1]
Androsterone	Log dose—comb growth	[illegible]	1 7	0.180	0.5	
Androsterone	Log dose—log comb growth	3	0 [illegible]68	0.197	0 0	Emmens[2]
Androsterone	Log dose—log comb growth	5	0.404	0 [illegible]80	0.125	
Androsterone	Log dose—comb growth	5	10	0.271	0 [illegible]00	McCullagh and Cuyler[4]

Application of androgens to capon's comb

If the hormone is applied directly to the comb instead of by intramuscular injection the amount necessary to produce a significant

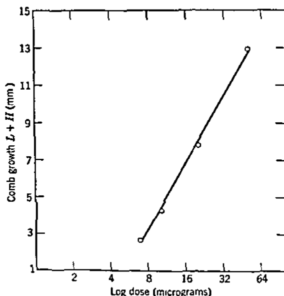


Fig 2 Capon's comb response to androsterone administered by daily comb inunction for 5 days (McCullagh and Cuyler[4])

increment in the comb is approximately one hundredth the amount needed by injection[4, 8, 43] Figure 2 illustrates the log dose response curve obtained from the data of McCullagh and Cuyler[4] when andros

5 days and the combs are again measured one day after the last dose The mean length plus height (L + H) for at least 8 capons may be referred to a standard curve and the unitage in international units (I U) read directly

The capon unit of Gallagher and Koch[1] was defined as the daily amount of material injected for 5 days which yielded a 5 mm average increase in (L + H) This unit is roughly equivalent to one I U which by formal definition represents the androgenic activity of 0 1 mg of pure androsterone (XXV) Gallagher and Koch reported a mean error of ±22 6 per cent when the unknown was run in parallel with a standard and a group of 16 to 25 capons was used for both unknown and standard

Greenwood et al [2] Emmens[3] and McCullagh and Cuyler[4] have studied the capon method of androgen assay They employed methods similar in details to the method of Gallagher and Koch[1] Figure 1

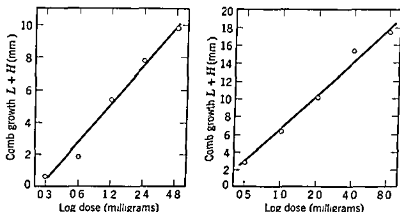


Fig 1 Capon s comb response to androsterone injected daily Left 3 day test right 5 day test (Greenwood et al [2])

illustrates the dose response curves found by Greenwood et al [2] for the 3 and 5 day assays Plotting the logarithm of the dose of androsterone (XXV) versus the response a linear relationship was found Using the 5 day assay method Greenwood et al [2] reported an accuracy of ±18 per cent ($P = 0\ 95$) if 5 capons are used for the unknown and referred to standard curve and ±12 per cent ($P = 0\ 95$) if 10 animals are used Table 1 summarizes the characteristics of the intramuscular injection capon method for both 3 and 5 day test periods Androsterone (XXV) was the androgen in each instance This table indicates the type of relationship the slope (b) the index of precision (λ) and the sensitivity[6]

The mean index of precision (λ) was 0 184 ± 0 063 Table 3 summarizes the characteristics of the inunction capon method

TABLE 3

SUMMARY OF ANDROGEN METHODS*

(Capon s Comb—Inunction)

Material	Relationship	Duration of Test (days)	Slope (b) ± S.E	Index of Precision (λ) ± S.E.	Sensitivity (μg)	References
Androsterone (XXV)	Log dose—comb growth	3	7 37 ± 0 4	0 184 ± 0 063	1 2	Emmens
Androsterone	Log dose—comb growth	5	30 3	0 0 6	7 0	McCullagh and Cuyler

Chick Methods

The early studies of Ruzicka[6] Burrows et al [7] Danby[8,9] Dorfman and Greulich[10] and Frank et al[11,12] indicated the possibility of using the chick comb as the test object for androgen assays Ruzicka[6] painted the chick s comb with a 0 5 per cent solution of androsterone (XXV) in oil each day for a period of several weeks and obtained large increases in comb area He did not however study this reaction quantitatively Frank and Klempner[1] applied the androgens in oil solutions directly to the base of the comb These workers were able to evoke a definite response with as little as 20 μg of androsterone Burrows and his co-workers[7] elicited comb growth both by injection into the base of the comb and by the intramuscular route In all the studies mentioned the end point depends on the weight of the comb These represent an improvement over the less exact methods of measurement of size of the capon s comb However in the latter instance there is the advantage of having each animal serve as its own control All in all the chick method is a much more practical procedure and has largely replaced the older capon assay

Relative reactivity of combs of various breeds

White Leghorn chicks are used for androgen assays because of their relatively high sensitivity Figure 3 illustrates the response of three breeds of chicks to testosterone propionate (LXXXIX) administered by direct application to the comb On the basis of the minimal quantity of testosterone propionate (LXXXIX) needed to produce a 20 per cent increase in the comb ratio the male White Leghorns were fifteen times as sensitive as the Rhode Island Reds and twenty times as sensitive as the Barred Rock Similarly the female White Leghorns were

terone (XXV) was applied directly to the comb The details are the same as described in the preceding section except for the administration of the androgen solution The extract is dissolved in sesame oil so that the total dose is contained in 1 ml of solution Each day for 5 consecutive days 0 2 ml of the androgen solution is applied evenly over the whole comb

Emmens[5] has studied the capon s comb method using inunction He used both White and Brown Leghorn capons The hormone is dissolved in 0 1 ml of oil and applied to the comb once daily for 3 days The combs are measured (L + H) with a millimeter rule before treatment is begun and again one day after the last hormone application

Table 2 presents the results of four assays using a total of 20 capons 10 on the unknown and 10 on the standard Emmens data[5] were

TABLE 2

THE ASSAY OF ANDROSTERONE (XXV) BY THE CAPON S COMB INUNCTION METHOD OF EMMENS[5]

(Based on the Data of Emmens[5])

$N = 5$

$$\frac{\text{High dose of standard}}{\text{Low dose of standard}} = \frac{\text{High dose of unknown}}{\text{Low dose of unknown}}$$

Standard = Unknown

Dosage Level (μg)	Combined Slope (b)	Index of Precision (λ)	Difference between Slopes (t)	Potency Ratio (% ± S E)
0 4 0 8	9 33	0 108	1 215	130 ± 16
0 4 1 2	6 88	0 360	0 084	92 ± 34
0 4 1 6	7 50	0 186	0 875	97 ± 19
0 8 1 6	5 83	0 079	2 610	119 ± 22

used and calculated according to the simplified statistical design of Bliss[5a] By using this design and appropriate statistical formulae measure of the potency ratio the error in the potency ratio and the significancy of differences in the slopes of unknown and standard are easily obtained Since the unknown and standard are identical the actual potency ratio is 100 per cent In the four tests the determined potency ratio varied from 92 ± 34 to 130 ± 10 In only one instance were the slopes of the unknown and standard significantly different

but the combs of the White Leghorns showed a significantly greater slope

An evaluation of the maximum percentage increase in comb size by androgen stimulation revealed that no significant difference could be demonstrated among the three breeds for either male or female chicks[13]

Method of Frank et al[14 1 16]

The technique devised by Frank et al[14 15 16] is simple sensitive and reproducible Using this method Dorfman[17] has shown that in 24 determinations of androsterone (XXV) in the dosage range of 20 to 40 μg and using 16 to 20 chicks per assay the mean error of the assays was 13 per cent and in 39 determinations over the range from 10 to 50 μg using the same number of animals per assay the mean error was 24 6 per cent The reliability of the method has been confirmed[17]

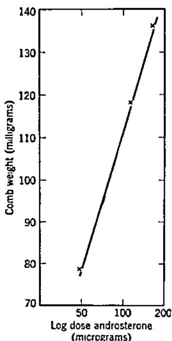


Fig 4 Chick s comb response to androsterone by direct application (Vallee et al[18])

PROCEDURE White Leghorn chicks mixed pullets and cockerels are used at 2 to 3 days of age The animals are kept in a brooder with a thermostatic control at a temperature between 88 and 96 F

Each group should consist of at least 16 chicks The total dose of material equivalent to an amount between 20 and 40 μg of androsterone (XXV) to be administered to each chick is dissolved in 0 35 ml of sesame oil Starting when the animals are 2 to 3 days of age 0 05 ml of oil is administered daily for 7 days The material is dropped on the comb by means of a 1 ml tuberculin syringe fitted with a fine hypodermic needle An attempt is made to apply the oil solution slowly so that spreading to the head feathers is minimized Twenty four hours after the last application of androgen solution the chicks are autopsied (8 to 9 days of age)

Body weights are determined at the time of the first application of the androgen At autopsy the body weight weight of comb and sex of the animal are determined The combs are removed by two longitudinal incisions along the base at the juncture with the scalp The incisions are extended vertically down to the skull The comb is freed

ten times as responsive as the Rhode Island Reds and twenty times as responsive as the Barred Rocks

The comparative sensitivities of the combs of the three breeds were evaluated by selecting portions of the log dose response curves where the slopes of all three breeds were not significantly different and

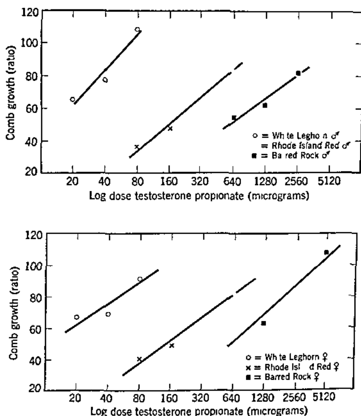


Fig 3 *Top* Comb responses of three breeds of male chicks to testosterone propionate *Bottom* Comb responses of three breeds of female chicks to testosterone propionate (Dorfman [13])

by using the displacement of the curves as another measure of the relative sensitivity of the various breeds If the sensitivity of the male White Leghorn chick comb was expressed as 100 per cent the sensitivity of the Rhode Island Red was 10 per cent and of the Barred Rock 1 8 per cent

A third criterion of sensitivity of the respective combs to androgen was the maximum slope attainable using a log dose response relationship for at least three points No significant difference in maximum slope was found for the Rhode Island Red and Barred Rock combs

TABLE 4

SUMMARY OF ANDROGEN METHODS

(Chick's Comb)

Material	Route	Relationship	Duration of Test (days)	Slope (b) ± S.E.	Index of Precision (λ) ± S.E.	Sensitivity	Ref.
Testosterone propionate (LXXXIX)	Application	Log dose—log comb weight	7	0.401 ± 0.033	0.250 ± 0.026	20 μg	Dorfman
Testosterone (VIII)	Application	Log dose—comb weight	7	103 ± 9	0.344 ± 0.038	50 μg	Dorfman
Testosterone propionate	Subcutaneous injection	Log dose—comb weight	5	6 9 ± 10.5	0.308 ± 0.033	500 μg	Dorfman
Methyltestosterone (XCVI)	Oral	Log dose—comb weight	10	160 ± 25	0.318 ± 0.028	5 mg per kilo food	Dorfman
Androsterone (XXX)	Application	Log dose—comb weight	[illegible]	44.1 ± 3.68	0.491 ± 0.033	15 μg	Vall et al.
Androsterone	Application	Log dose—comb weight	7	115.1	0.244	50 μg	

from the skull and its base is touched lightly to a towel to remove blood from the cut surface The comb is weighed quickly to avoid drying on a suitable torsion balance

To calculate the concentration of androgens in terms of androsterone (XXV) the following formula was used where Σw = sum of comb weights in mg Σw = sum of the comb weights squared ΣB_1 = sum of initial body weights in grams ΣB_t = sum of terminal body weights in grams Nm = number of male chicks and Nf = number of female chicks The androsterone (XXV) equivalents (A) in micrograms are calculated by the following formula

$$A = \frac{1\,061(\Sigma w) - 0\,0043(\Sigma w^2) - 0\,397(\Sigma B_1) + 14\,75 Nm + 18\,54 Nf}{Nm + Nf}$$

Additional chick comb methods

In addition to the method described by Frank et al [14,16] the chick comb has been used under a variety of conditions for several different androgens Valle et al [18] have studied androsterone (XXV) by direct application (Fig 4) Dorfman has studied the assay of testosterone propionate (LXXXIX) by direct application [17] testosterone propionate (LXXXIX) by injection [19] testosterone (VIII) by application [5] (Fig 5) and methyltestosterone (XCVI) by oral administration [5,19] (Fig 6)

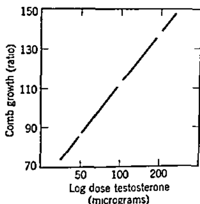


Fig 5 Chick s comb response to testosterone by direct application Dorfman [5])

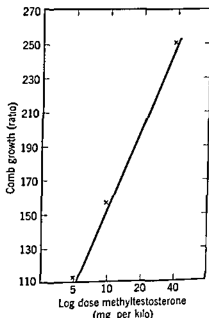


Fig 6 Chick s comb response to methyltestosterone administered orally (Dorfman [5,19])

of rats for each of the four solutions two groups on the unknowns and two groups on the standards Each group should contain eight to twelve animals Each animal receives one subcutaneous injection of 0 1 ml of the proper oil solution Seventy two hours after the injection of the test solutions the seminal vesicles and prostate are removed by incising with iridectomy scissors at a point near the base of the bladder The tissue is dipped in physiological saline and placed on a cork board under a dissecting microscope The coagulating glands are teased from the seminal vesicles and the latter are again immersed in saline dried on blotting paper for a few seconds and weighed rapidly on a torsion balance

The weights of the seminal vesicles are used in the calculations according to Bliss method[38] By these calculations the following are determined the potency ratio of the unknown and standard the error range of the potency ratio and the significancy of difference between

TABLE 5

ANDROGEN ASSAY OF TESTOSTERONE PROPIONATE (LXXXIX)

(U S P INTERLABORATORY TRIALS)

Lab No	Strain	5.00 mg /cc (Theoretical)					3.50 mg / cc (Theoretical)				
		Found (mg /cc.)	±S.E	b	λ	t	Found (mg / cc)	±S.E	b	λ	t
1	Wistar	4 43	±0 81	17 32	0 51	1 037	2 33	±0 0	14 60	0 53	0 149
							3 0	±0 60	17 10	0 8	0 69
	Wistar	4 80	±1 3	13 1	0 3 6	1 3 9	3 8	±0 39	14 5	0 145	1 438
							2 99	±1 06	11 12	0 4 7	1 882
3	Wistar	4 95	±0 0	12 94	0 139	1 0	2 90	±0 40	11 69	0 1 6	0 154
		4 90	±0 47	13 16	0 132	1 891	3 26	±0 21	14	0 089	0 91
							3 66	±0 7	13 7	0 100	1 556
							3 08	±0 70	14 2	0 092	0 7 3
4	Osborne-Mendel	5 10	±0 53	17 5	0 14	1 404	3 88	±0 41	1 65	0 139	0 040
							4 00	±0 51	15 74	0 173	0 0 9
5	Hooded	4 3	±0 7	15 2	0 24	0 608	3 46	±0 84	10 97	0 334	0 5 7
		5 1	±1 34	11 23	0 3	0 48	83	±0 5	11 40	0 2 7	1 985
							1	±0 81	10 91	0 3 6	1 591
							98	±0 61	10 9	0 65	0 3 1
6	Wistar	4 48	±0 85	10 09	0 6	0 6 9	2 91	±0 63	14 29	0 299	1 480
							2 75	±0 35	17 03	0 161	4 2 0
7	Harlan	5 35	±0 60	5 90	0 154	2 31	4 32	±0 47	29 6	0 147	0 868
		4 40	±0 3	4 85	0 8	0 5	4 8	±1 11	17 1	0 319	1 930
							3 98	±0 48	27 6	0 163	1 83
							5	±0 84	23 3	0 18	1 6
8	Holtzman	6 30	±0 67	16 94	0 142	0 458					

Unknown *A* (00 mg /) Found (11 trials) Mean = 5.01 Range = (4 40–6.30)

Unknowns *B* and *C* (3 5 mg /) Found (0 trials) Mean = 3 48 Range = (.33–5. 5)

A summary of the chick comb methods is included in Table 4 This table indicates the various characteristics of each particular assay including the measure of precision stated as λ and the minimum quantity of material that can be assayed

SPARROW S BILL Androgens cause blackening of the English sparrow s bill (see Chapter 13) This end point has not been studied from a quantitative viewpoint but the sensitivity has been demonstrated to be of an extraordinary high degree Thus a total of 1 μg of testosterone (VIII) administered in sixteen divided doses produced positive responses in four of six castrated males and a similar dose of androsterone (XXV) produced positive responses in all of a group of five castrated males [20]

Mammalian Assays

The methods involving the mammal have been many and varied The most important from the point of view of sensitivity and reproducibility have been those which employ the weight responses of the seminal vesicles prostate or both The studies of Korenchevsky and Dennison [1] Deanesly and Parkes [22] Miescher et al [23] Callow and Deanesly,[24] Bulbring and Burns, [5] and Greene and Burrill [6 27] are important in the development of these methods Less defined methods include the electrical ejaculation test [9-31] ductus deferens test [32] histology of Cowper s gland [33 35] and a pharmacological ejaculation test using pernoston and yohimbine [36]

The mammalian end points are less sensitive to androgens than are those of the fowl The sensitivity of the test in fowls may be increased by applying the test material directly to the comb The method described here is one which has been carefully enough studied to justify its use where a reliable procedure of known range of error is required The method is too insensitive for routine assay of urinary extracts

Seminal vesicle method (Mathieson and Hays [37])

Male rats weighing 40 to 75 grams are castrated when they are 26 to 29 days old At least 14 days are allowed between the operation and the use of the animals in the assay Two standard solutions are prepared containing 2 0 and 8 0 mg of testosterone propionate (LXXXIX) per ml of oil Sesame or corn oil may be used Two unknown solutions are prepared so that they contain approximately the same concentrations of testosterone propionate (LXXXIX) as the standard solution The concentrations of unknowns and standards should both be in a ratio of 4 to 1 between the high and low doses

The castrated rats are divided into four equal groups one group

9 Danby M *Endocrinology* 27 236 1940
10 Dorfman R I and W W Greulich *Yale J Biol Med* 10 79 1937
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38 Bliss C I *Science* 100 577 1944
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41 Dorfman R I and A S Dorfman *Endocrinology* 42 1 1948
42 Dessau F *Acta Brevia Neerl Physiol Pharmacol Microbiol* 5 139 1935
43 Fussganger R *Med u chem* Z 2 194 1934

the slopes of the unknown and standard Table 5 summarizes the results of some typical assays using this method [39]

In 1949 Wilk et al [40] found that the method of Mathieson and Hays [37] might be improved both with respect to precision and sensitivity by administering the hormone intramuscularly instead of subcutaneously

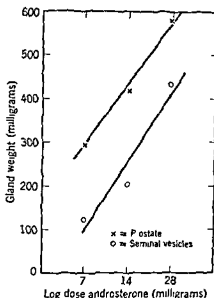


Fig 7 Responses of prostate and seminal vesicles to androsterone administered over a 14 day period (Callow and Deanesly [24])

Figure 7 illustrates the typical response of the seminal vesicles and prostate to androsterone (XXV) The relationship is log dose (mg) to accessory weight (mg) [24]

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One hundred ml of absolute alcohol are measured into a glass stoppered Pyrex bottle and chilled in crushed ice Two lots of 15 mg each of ascorbic acid are weighed The first lot is ground up with small successive portions of absolute alcohol and added to the chilled alcohol Since ascorbic acid is sparingly soluble in ethanol it is added as a fine suspension This must be done before dissolution of the solid potassium hydroxide and again after filtering the resultant cloudy solution Twenty five to 30 grams of finely powdered potassium hydroxide pellets are added next A stream of nitrogen is bubbled gently through the mixture for 5 seconds the stopper replaced under nitrogen and the bottle shaken vigorously for about 5 minutes It is necessary to shake until a concentration of at least 2.6 N is reached After the mixture is sampled to test the normality the air space is again flushed with nitrogen if further shaking is required The solution is filtered through a fine porosity Buchner type Pyrex glass fitted filter into a 250 ml Pyrex suction flask packed in crushed ice A gentle stream of nitrogen is played over the surface of the filtering fluid from a conical funnel The second lot of 15 mg of ascorbic acid is ground with absolute alcohol and added to the filtered solution The final concentration of the cold alkali is then adjusted to 2 5 *N* within 1 per cent A slight turbidity from the ascorbic acid may be disregarded The reagent is stored in the cold under nitrogen Thereafter the air space is always flushed with nitrogen after the bottle has been opened

PROCEDURE Into one tube which will serve as a blank are measured in succession 0 2 ml of absolute ethanol 0 2 ml of *m* dinitrobenzene solution and 0 2 ml of potassium hydroxide solution The reagents are similarly added to the unknown contained in 0 2 ml of absolute ethanol It is convenient to add the reagents from a microburette calibrated to 0 01 ml The exact time of adding the potassium hydroxide solution is noted The tubes are well shaken to disperse the dense potassium hydroxide solution lightly stoppered and placed in a water bath kept at 25 ± 0 1°C The tubes are shielded from all but dull diffused light. After an hour 10 ml of absolute ethanol are added to each tube and the contents mixed and read in a suitable photoelectric colorimeter with light at 5200 A. It is desirable to complete all measurements of a group of samples within 5 minutes of the time of dilution with absolute ethanol. The 17 ketosteroid content of the test material is determined from the E_{5200} value by reference to a calibration curve constructed from measurements with androsterone (XXV) or dehydroepiandrosterone (XXIII)

APPENDIX D

Chemical Assay Methods

Determination of 17 Ketosteroids

Method A (Callow, Callow and Emmens [1])

REAGENTS *m Dinitrobenzene* Well crystallized and fairly pure *m* dinitrobenzene is further purified as follows 20 grams are dissolved in 750 ml of 95 per cent alcohol warmed to 40° and 100 ml of 2 *N* NaOH are added After 5 minutes the solution is cooled and 2500 ml of water are added The precipitated *m* dinitrobenzene is collected on a Buchner funnel washed very thoroughly with water sucked dry and recrystallized twice in succession from 120 ml and 80 ml of absolute alcohol The material must be well crystallized in almost colorless needles m p 90 5 to 91° Admixture of a 1 per cent alcoholic solution with an equal volume of aqueous 2 *N* NaOH should give no color after an hour The reagent is a solution of this material (2 grams per 100 ml) in absolute alcohol Stored in a brown stoppered bottle in the dark it is stable for 10 to 14 days After this time it does not produce a maximum color intensity in the ketosteroid reaction

Potassium Hydroxide The reagent solution is 2 5 *N* KOH in absolute alcohol Nine or 10 grams of KOH are dissolved with mechanical stirring in 50 ml of absolute alcohol and the solution is filtered through a hardened paper (Whatman No 50) on a suction pump The concentration is checked by titration of 0 5 ml with 0 1 *N* H_2SO_4 (methyl orange indicator) and the solution is diluted with alcohol if necessary to bring it within the limits of 2 48 and 2 52 *N* The solution is stable for 2 to 5 days if stored in a refrigerator It must be discarded as soon as the faintest color is perceptible

Wilson and Carter [2] have reported that the 2 5 *N* potassium hydroxide alcoholic solution can be kept for a period of 3 to 4 months if ascorbic acid is added and if the reagent is kept in an atmosphere of nitrogen This modified reagent is prepared as follows

same reaction was found to take place with androsterone succinate (XC) and androsterone sulfate (LXXVIII) Dehydroepiandrosterone (XXIII) 3-ketones such as testosterone (VIII) and cholestenone (XXVII) 20-ketones such as allopregnan-3α-ol 20-one (CI) and pregnan-3α-ol 20-one (XCIII) do not give the typical color Only a weak yellow color is developed by the 3 17 diketone Δ^4 androstene-3 17 dione (LXI) and 3 20 diketone progesterone (XCIV)

The Pincus reaction gives values of 60 to 68 per cent of the titer found by the Zimmermann reaction when applied to the neutral ketonic fraction of normal men s and women s urine

PROCEDURE A solution of 3 8 grams of antimony trichloride (C P) in a mixture of nine parts of glacial acetic acid (C P) to one part of acetic anhydride (C P) constitutes the reagent Then 0 2 ml of the reagent is added drop by drop to a dried steroid or urinary extract contained in a test tube The tube is stoppered and heated for 20 minutes in a boiling water bath Within ½ to 1 minute after the test tube is immersed in the water bath the tube is thoroughly shaken to insure complete solution After being heated the tube is cooled and the solution diluted with a mixture of 95 parts of glacial acetic acid and 5 parts of water The diluent is added slowly with shaking The typical color with maximum intensity is attained after standing 40 to 60 minutes after dilution at room temperature The tube are read in a photoelectric colorimeter at 6100 Å between 40 and 60 minutes after dilution Androsterone (XXV) is used for the standard reference curve

Determination of Dehydroepiandrosterone

Patterson reaction [6]

One fifth of a total neutral extract from a 24 hour urine sample is evaporated to dryness in a test tube To the residue is added 1 ml of concentrated sulfuric acid and the tube is shaken until the extract is completely dissolved The tube is then kept at 25 C for 20 minutes and 1 ml of distilled water is added drop by drop down the side while the tube is kept cool by shaking it in cold water The tube is then heated in a boiling water bath for 1 minute A blue or blue violet color developing in the final stage indicates the presence of excess dehydroepiandrosterone (XXIII) or closely related steroids The color is very stable and unaltered by several minutes heating

The reaction is sensitive to 0 1 mg of dehydroepiandrosterone (XXIII)

If a correction for nonspecific chromogens (mostly present in the nonketonic fraction) is desired readings should be done in both the violet (4200 Å) and in the green (5200 Å) The corrected reading in the green is calculated by the following formula

$$\text{Corrected reading at } 5200\ \text{Å} = \frac{K_i E_g - E_v}{K_i - K_s}$$

where E_g = observed extinctions at 5200 Å

E_v = observed extinctions at 4200 Å

$K_i = \frac{E_v}{E_g}$ for chromogens

$K_s = \frac{E_v}{E_g}$ for pure 17 ketosteroid

Method B (Holtorff and Koch[3])

The reagents consist of a 2 per cent solution of *m* dinitrobenzene in 95 per cent redistilled ethanol and 5 00 *N* aqueous potassium hydroxide (electrolytic grade) The latter solution should be protected with a paraffin seal to prevent any significant accumulation of carbonate

PROCEDURE Into a photometer tube are accurately measured 0 2 ml of solution or 0 2 ml of redistilled 95 per cent EtOH for blank 0 2 ml of *m* dinitrobenzene solution and 0 2 ml of 5 0 *N* KOH solution The tubes are then corked gently shaken and placed in a water bath for 90 minutes at 25° ± 0 2° At the end of 90 minutes the solution is diluted with 10 ml of redistilled 95 per cent ethanol After the outside of the tube is dried and polished it is placed in a rack for 3 minutes and the optical density is measured after the zero density point of the photometer is set with the blank The 17 ketosteroid content of the test material is determined from the E_{00} value by reference to a calibration curve constructed from measurements with androsterone (XXV) or dehydroepiandrosterone (XXIII) It has frequently been found advisable to run standards with each test run

Method of Pincus[4]

PRINCIPLE An intense blue color (with an absorption maximum at 6100 Å) is developed by such 17 ketosteroids as androsterone (XXV) epiandrosterone (XXI) etiocholan 3α ol 17 one (XXII) and $\Delta^{2,3}$ androsten 17 one (LII) by heating with a concentrated antimony trichloride solution followed by dilution with glacial acetic acid The

Filter 660, the wavelength of maximum absorption of the colored product. A center setting is obtained by adjusting the "blank without furfural" to 100. Since all the solutions containing furfural increase slightly in color while standing at room temperature, the colorimetric measurements are made at approximately the same time interval (± 10 minutes) after removal from the bath.

TABLE 1

*Reagents for Dehydroepiandrosterone (XXIII) Determination**

	Glacial Acetic Acid (ml.)	DHA Standard Solution (ml.)	50 Per Cent Acetic Acid (ml.)	Furfural Solution (ml.)	Urine Extract in Glacial Acetic Acid (ml.)
Blank without furfural	0.5		2.0		
Reagent blank	0.5			2.0	
DHA (XXIII) standards (*10, 30, and 50 µg. levels*)		0.5		2.0	
Urine extract blank			2.0		0.5
Urine extract				2.0	0.5

There is a small but significant day to day variation in the color intensity developed by DHA standards even though the same reagents are used and the assay conditions are apparently identical. It is therefore essential that a full set of standards be included in each assay series. The color produced is affected significantly by changes in furfural concentration, H_2SO_4 concentration, bath temperature, and heating time. Therefore it is also essential to use the same reagents and assay conditions for standards, blanks, and extracts.

CALCULATIONS. (1) The galvanometer readings (G) are converted to L values ($L = 2 - \log G$). (*A convenient table for conversion is* included in the manual accompanying the Evelyn colorimeter.) *If replicate determinations have been made, the mean L value for each* set of replicates is calculated.

(2) *To eliminate nonspecific color (a) originally present in the* extract and (*b*) produced by the action of H_2SO_4 alone on the extract, the L value for the "urine extract blank" is subtracted from that of the "urine extract." Occasional urine extracts develop a slight turbidity which also is corrected by the urine extract blank. The mean L values of the reagent blank and the DHA standards are plotted on graph paper, and a curve is drawn connecting the points. (The curve deviates slightly from strict linearity, thus differing from that obtained in the analysis of cholic acid.) The DHA content of the urine extract

Method of Munson et al [6]

REAGENTS (1) *Furfural solution* A commercial grade of furfural is distilled twice on a boiling water bath under reduced pressure The middle fraction only is retained from each distillation For a satisfactory product it is essential that the temperature of a boiling water bath not be exceeded The nearly colorless product is promptly dissolved in 50 per cent acetic acid at a concentration of 0 56 per cent (volume per volume) and stored in the cold The reagent stored at −5° is stable for many months

(2) *Standard solutions of dehydroepiandrosterone (XXIII) (DHA)* A solution containing 10 mg of DHA or 11 45 mg of DHA acetate per 100 ml of glacial acetic acid is prepared and additional standards containing 0 060 and 0 020 mg of DHA per ml are obtained by dilution with glacial acetic acid Because DHA crystallizes in two polymorphic modifications the melting point is an unsatisfactory criterion of purity For the greater portion of the work the acetate of this compound (m p 169 to 170 5° (corrected) $[\alpha]_D = +4\,2°$ (ethanol)) was used as the standard but the results were expressed in terms of DHA The acetate gives the same intensity of color mole for mole as the free hydroxy ketone

(3) *Sulfuric acid 16 0 N*

(4) *Acetic acid 50 per cent by weight*

Provided that all test solutions are treated uniformly minor changes in reagent concentrations temperature and time are relatively unimportant

An amount of pure steroid or of urine extract estimated to contain 10 to 50 μg of DHA *or its equivalent is transferred to a calibrated* Evelyn colorimeter tube and evaporated to dryness on a water bath under a stream of nitrogen The dry residue if the evaporation has been properly carried out is confined to a small area in the bottom of the tube and is dissolved in 0 5 ml of glacial acetic acid with warming if necessary The solutions in Table 1 are then added to Evelyn tubes (or equivalent) in duplicate or triplicate and mixed

To each tube indicated in Table 1 7 5 ml of 16 *N* sulfuric acid are added at 1 minute intervals After the contents are mixed well the tube is placed in an efficient large capacity constant temperature water bath maintained at 67 ± 0 2° After exactly 12 minutes in the bath the tube is removed and immediately placed in an ice bath for 1 minute After all the tubes have been heated and cooled (a series of thirty to forty tubes can be analyzed conveniently) the color intensity is determined in the Evelyn colorimeter (or equivalent) with

Determination of Testosterone and Testosterone Propionate

Assay of testosterone propionate in oil[9]

Frequently particularly with commercial solutions it is necessary to assay relatively concentrated solutions of testosterone propionate (LXXXIX) in oil A chemical method which is quantitative and convenient has been suggested for this purpose[9]

PREPARATION OF SEMICARBAZIDE ACETATE STOCK SOLUTION A semicarbazide acetate solution (0 225 molar) is prepared by refluxing together for 2 hours 2 5 grams of semicarbazide hydrochloride 2 5 grams of anhydrous sodium acetate and 30 ml of methanol The solution is chilled and filtered to remove sodium chloride The filtrate is made up to a volume of 100 ml with methanol This solution is stable when kept refrigerated and protected from light If it turns yellow it should be discarded.

PREPARATION FOR ASSAY OF SOLUTIONS CONTAINING LESS THAN 10 MG OF TESTOSTERONE PROPIONATE (LXXXIX) PER ML. Petroleum ether and 90 per cent ethanol are equilibrated by shaking together equal volumes of the solvents The mixture is permitted to stand and the two layers are separated An oil solution containing 50 mg of testosterone propionate (LXXXIX) is accurately measured and added to 40 ml of the equilibrated petroleum ether contained in a separatory funnel After being mixed thoroughly the petroleum ether solution is extracted eight times with 20 ml portions of the equilibrated 90 per cent ethanol The combined ethanol extracts are evaporated almost to dryness transferred quantitatively with methanol to a 50 ml round bottomed flask, and evaporated to complete dryness The residue is analyzed as described under "Assay of Testosterone Propionate" which follows

ASSAY OF TESTOSTERONE PROPIONATE An accurately measured portion of a solution containing 50 mg of testosterone propionate (LXXXIX) is transferred into a 50 ml round bottomed flask If the testosterone propionate (LXXXIX) solution contains less than 10 mg per ml a preliminary separation is done as directed in the section described above Three ml of 0 225 *M* semicarbazide acetate solution are added to the 50 ml round bottomed flask fitted with a reflux condenser and the mixture is refluxed vigorously for 2 hours The flask is cooled slowly to room temperature 10 ml of iso octane are added and the contents are mixed The mixture is then added with stirring to 75 ml. of ice-cold water contained in a 150 ml beaker The flask is rinsed with two 5 ml portions of iso octane If any material re

aliquot is estimated by interpolation on the graph and the total DHA content of the extract is obtained by application of the appropriate factor

Method of Jensen [7,8]

The following method for the determination of dehydroepiandrosterone (XXIII) has been suggested by Jensen to determine this constituent quantitatively An important point is the hydrolytic procedure which according to the author permits the preparation of an extract which concentrates the total dehydroepiandrosterone in the urine with negligible amounts of artifacts

HYDROLYSIS AND EXTRACTION An aliquot of a 24 hour sample of urine between pH 4 and 10 estimated to contain sufficient steroid for analysis is heated for 8 hours at 96 ± 2°C and then extracted with ethyl ether (see p 528) The ether extract is washed successively one time with 20 ml of 2 N sulfuric acid two times with 20 ml portions of 4 N sodium hydroxide and three times with 20 ml portions of distilled water The washed ether solution is dried over one gram of anhydrous sodium sulfate and concentrated to dryness

COLORIMETRIC ANALYSIS

Reagent 1 Four volumes of concentrated sulfuric acid plus one volume of peroxide free ethyl ether

Reagent 2 Peroxide free ethyl ether

The dried residue from the procedure above is dissolved in 2 5 ml of reagent 1 and heated for 85 seconds without being stirred in a boiling water bath The reaction mixture is cooled in ice water and stirred with a glass rod The test tube is placed in a stand and 5 ml of reagent 2 are added with mixing After standing 3 to 15 hours at room temperature the solutions are read at 6000 (maximum), 5330 and 4700 Å

SAMPLE CALCULATIONS

	Reading		
	E_{4700}	E_{5300}	E_{6000}
50 μg of dehydroepiandrosterone			0.613
1/100 of a 24 hour urine sample	0.216	0.342	0.514

E_{6000} corrected

(1) 0.613

(2) $0.514 - \frac{0.216 + 0.342}{4} = 0.374$

$\frac{374 \times 100}{20 \times 613} = 3.05$ mg /24 hours determined as of dehydroepiandrosterone.

testosterone (XIX) androstane 3 17 dione (LVIII) dehydroepiandrosterone (XXIII) Δ^5 androstene-3β 17β diol (XLIX) androsterone (XXV) cortisone (CXVI) epiandrosterone (XXI) progesterone (XCIV) cholesterol (XIII) estradiol 17β (L) estrone (XLV) and estriol (XLIV)

METHOD A 10 ml graduated test tube containing the testosterone (VIII) (either dry or in about 0 4 ml of 95 per cent alcohol) is placed in an ice bath Two ml of concentrated sulfuric acid are added and mixed with a footed stirring rod care being taken to avoid spattering The tube is heated for 2 minutes in boiling water without stirring and then placed in an ice water bath After 5 minutes 2 ml of saturated aqueous thiocol (recrystallized from 60 per cent ethanol) and 0 3 ml of 1 per cent aqueous copper sulfate are added with stirring The tubes are reheated in boiling water for 2 minutes During this period they are stirred three times The tubes are again placed in the ice water bath and diluted to the 10 ml mark with 50 per cent sulfuric acid. After being transferred to a colorimeter tube the solution is read against a blank containing the reagents but not the hormone in an Evelyn colorimeter equipped with a 6350 A filter

The production of the green compound apparently involves an oxidation Some green color is produced if the solution without copper or iron salts is vigorously stirred in the boiling water bath Copper sulfate is used to accelerate this reaction because it produces the most consistent results When ferric chloride is used the green color tends to fade when a small excess is added A relatively large excess of copper sulfate can be added without any fading Stronger oxidizing agents such as hydrogen peroxide and potassium permanganate destroy the green color

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mains in the flask it could be transferred with two 2 ml portions of *methanol* The contents of the beaker are mixed thoroughly and permitted to stand at 0 to 5°C for 2 to 3 hours Crystals of *testosterone* propionate semicarbazone will collect at the interface between the iso octane and aqueous layer

A vacuum flask for vacuum filtration is equipped with a previously dried (105°) and tared medium porosity fritted Pyrex glass funnel of about 30 ml capacity With the vacuum disconnected enough water is put on the filter to cover the fritted surface The mixture is poured carefully from the beaker into the funnel in a manner that will not mix the layers The layers are allowed to settle in the funnel so that the aqueous phase just above the fritted disc is clear Vacuum is applied just long enough to pull through most of the clear water layer but without permitting the crystals to reach the fritted disc This process is repeated several times until the contents of the beaker are completely transferred to the funnel Vacuum is applied long enough to pull through the entire remaining water layer and form a cake of crystals on the fritted disc Ten ml portions of iso octane and a policeman are used to transfer crystals which adhere to the sides of the beaker These portions also serve to wash the crystals which are on the filter Another 10 ml portion of iso octane is used to rinse the walls of the funnel and slurry the crystals The cake of crystals is sucked dry with the vacuum The crystals are washed with 20 to 30 ml of water and sucked dry using vacuum This procedure is repeated using about 10 ml of iso octane in place of the water The funnel and the crystals are dried to constant weight at 105° If the weight is high at this point it may be due to entrapped oil and it is necessary to rewash with iso octane and redry until the weight is constant.

The melting point of the semicarbazone crystals is determined in a bath heated at 3 per minute inserting the capillary at 200° Testosterone propionate semicarbazone melts between 207 and 217° with decomposition and the formation of a bright red color

$$\text{Calculation} \quad \frac{\text{mg of semicarbazone recovered}}{\text{ml of sample}} \times \frac{344\ 48}{401\ 53}$$

$$= \text{mg of testosterone propionate per ml}$$

Determination of testosterone [10]

A method for the quantitative determination of testosterone (VIII) [and Δ^4 androstene-3 17 dione (LXI)] has been described by Koenig et al.[10] The following steroids do not react with the reagent ethynyl

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